PCT/EP03/15799

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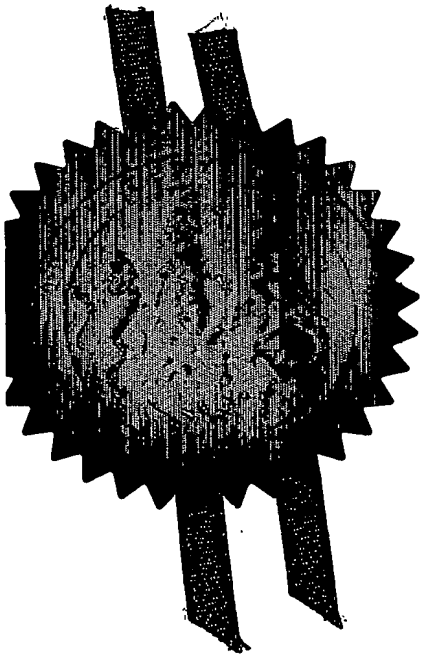

Signed 

Dated 29 October 2003

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090EC02 E76932 -1 D01030
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1.	Your Reference	**KC/SJB/PG5041**
2.	Patent application number *(The Patent office will fill in this part)*	0228552.6
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**GLAXO GROUP LIMITED** **GLAXO WELLCOME HOUSE** **BERKELEY AVENUE** **GREENFORD** **MIDDLESEX** **UB6 ONN** **GB**
	Patents ADP number *(if you know it)*	4735867003
	If the applicant is a corporate body, give the country/state of its corporation	**GB**
4	Title of the invention	**CHEMICAL COMPOUNDS**
5	Name of your agent *(if you know one)*	**KAREN CRAWLEY**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**GLAXOSMITHKLINE** **CORPORATE INTELLECTUAL PROPERTY (CN9 25.1)** **980 GREAT WEST ROAD** **BRENTFORD** **MIDDLESEX**
	Patents ADP number *(if you know it)*	**TW8 9GS** 8072555006

6 DEC 2002

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Description	61
Claim(s)	2
Abstract	2
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature KAREN CRAWLEY **06 December 2002**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

AMANDA WILKINSON
020 8047 4493

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a) *Notes*

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b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form*

If you have answered "Yes" Patents Form 7/77 will need to be filed.

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CHEMICAL COMPOUNDS

Field of the Invention

The present invention relates to a novel class of chemical compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a thombin inhibitor is indicated.

Background of the Invention

Thrombin is a serine proteinase present in plasma. It is converted from prothrombin into thrombin by Factor Xa a member of the trypsin-like serine protease class of enzymes. Thrombin plays a central role in the mechanism of blood coagulation by converting the soluble plasma protein, fibrinogen, into insoluble fibrin. The insoluble fibrin matrix is required for the stabilisation of the primary hemostatic plug. Many significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction and unstable angina. Both treatment of an occlusive coronary thrombus by thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) are often accompanied by an acute thrombotic reclosure of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the venous vasculature which can result in reduced blood flow to the affected extremity and a pre-disposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterised by the rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the vasculature leading to widespread organ failure.

Beyond its direct role in the formation of fibrin rich blood clots, thrombin has been reported to have profound bioregulatory effects on a number of cellular components within the vasculature and blood, (Shuman, M.A., Ann. NY Acad. Sci., 405: 349 (1986)).

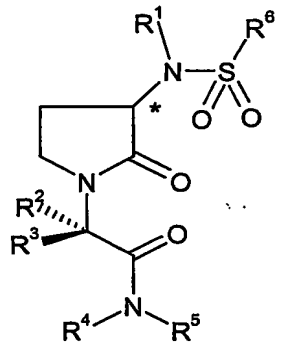
The inhibition of thrombin has been implicated as a potential treatment for a number of disease states. A thrombin inhibitor may be useful in the treatment of acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial

occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke. They may also have utility as anti-coagulant agents both in-vivo and ex-vivo, and in oedema and inflammation. Thrombin has been reported to contribute to lung fibroblast proliferation, thus, thrombin inhibitors could be useful for the treatment of some pulmonary fibrotic diseases. Thrombin inhibitors could also be useful in the treatment of tumour metastasis, preventing the fibrin deposition and metastasis caused by the inappropriate activation of Factor Xa by cysteine proteinases produced by certain tumour cells. Thrombin can induce neurite retraction and thus thrombin inhibitors may have potential in neurogenerative diseases such as Parkinson's and Alzheimer's disease. They have also been reported for use in conjunction with thrombolytic agents, thus permitting the use of a lower dose of thrombolytic agent.

Patent Applications PCT.GB02.02586 and PCT.GB02.02721 disclose certain FXa inhibitors including (E)-2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide and (E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide.

Summary of the Invention

The present invention provides compounds of formula (I):



(I)

wherein:

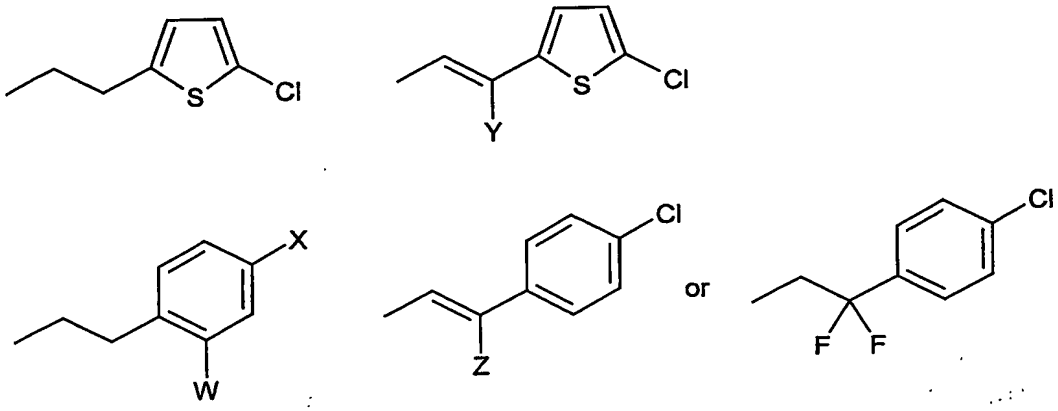
R^1 represents hydrogen, methyl, $-CH_2CO_2H$, $-CH_2CO_2C_{1-2}$alkyl, or $-CH_2CONR^7R^8$;

R^2 represents $-C_{1-4}$alkyl, $-CH_2CO_2H$, $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CON(CH_3)_2$, benzyl, $-CH_2CO_2$-benzyl, $-CH_2CO$-morpholine, or $-CH_2$-thiophene;

R^3 represents hydrogen;

R^4 and R^5 together with the nitrogen atom to which they are attached form a morpholino ring;

R^6 represents a group selected from:



wherein W represents H, Cl or F;
X represents Cl, Br, F or $-CH_3$;
Y represents CH_3 or CF_3;
Z represents $-CH_3$ or F;
R^7 and R^8 are independently hydrogen or methyl;
and pharmaceutically acceptable derivatives thereof.

Further aspects of the invention are:

- A pharmaceutical composition comprising a compound of the invention together with a pharmaceutical carrier and/or excipient.
- A compound of the invention for use in therapy.
- Use of a compound of the invention for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a thrombin inhibitor.
- A method of treating a patient suffering from a condition susceptible to amelioration by a thrombin inhibitor comprising administering a therapeutically effective amount of a compound of the invention.

Detailed Description of the Invention

The compounds of formula (I) contain chiral (asymmetric) centres. The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are within the scope of the present invention. Preferably, at the position marked "*" the stereochemistry is (S)-stereochemistry. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention.

Preferably, R^1 represents hydrogen, methyl, $-CH_2CO_2C_{1\text{-}2}$alkyl, or $-CH_2CONR^7R^8$. More preferably, R^1 represents hydrogen.

Preferably, R^2 represents methyl, ethyl, 2-propyl, i-butyl, s-butyl, $-CH_2CO_2H$, $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CON(CH_3)_2$, benzyl, $-CH_2CO_2$-benzyl, $-CH_2CO$-morpholine, or $-CH_2$-thiophene;

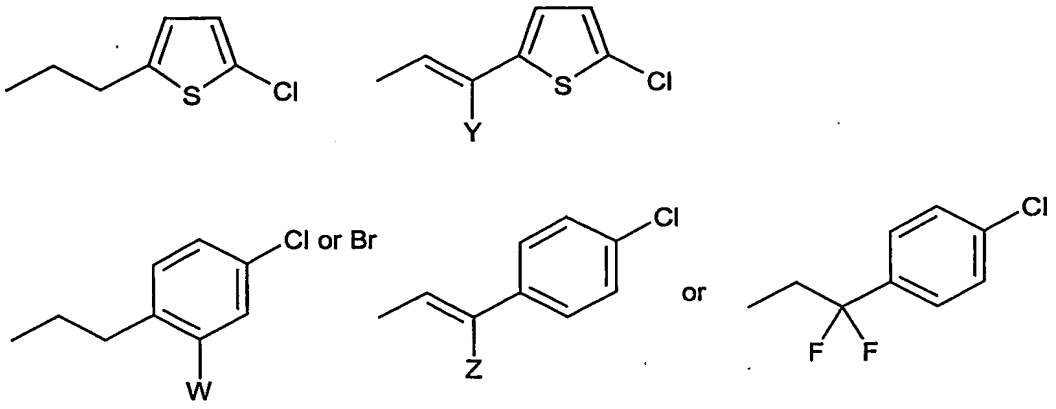
Preferably X represents Cl, Br or $-CH_3$. More preferably, X represents Cl or Br. Most preferably, X represents Cl.

Preferably W represents H.

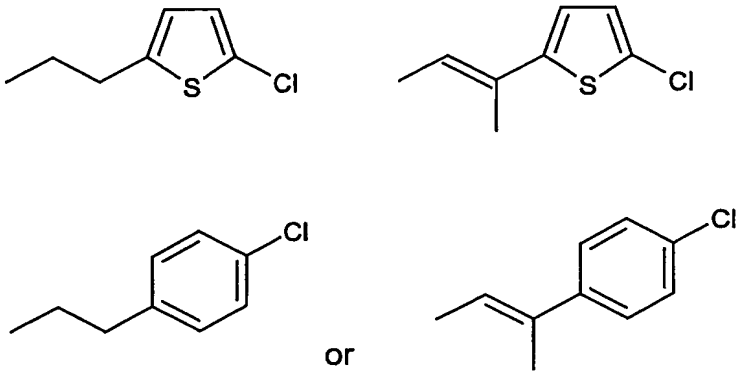
Preferably Y represents $-CH_3$.

Preferably Z represents $-CH_3$.

Preferably, R^6 represents a group selected from:



More preferably, R^6 represents a group selected from:



It is to be understood that the present invention covers all combinations of preferred groups described hereinabove.

As used herein, the term "thrombin inhibitor" means a compound which possesses thrombin inhibitory activity. Preferably, the thrombin inhibitor has a Ki (nM) of less than 200, more preferably less than 100, even more preferably less than 50, even more preferably less than 25, most preferably less than 10 when measured in accordance with the assay described hereinbelow. In comparison, prior art compounds (E)-2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide and (E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide have thrombin Ki (nM) of greater than 200. In a preferred aspect of the invention, the thrombin inhibitor is a "dual thrombin-Factor Xa inhibitor". In another preferred aspect of the invention, the thrombin inhibitor is a "selective thrombin inhibitor".

As used herein, the term "dual thrombin-Factor Xa inhibitor" means a compound which has inhibitory activity at both thrombin and Factor Xa.

As used herein, the term "selective thrombin inhibitor" means a compound which is selective for thrombin over Factor Xa.

The term 'alkyl' as used herein means both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl ($-CH_3$), ethyl ($-C_2H_5$), propyl ($-C_3H_7$) and butyl ($-C_4H_9$).

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate, or salt or solvate of such a prodrug, of a compound of formula (I), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I), or an active metabolite or residue thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles And Practice, which is incorporated herein by reference. Preferred pharmaceutically acceptable derivatives are salts and solvates.

Suitable salts according to the invention include those formed with both organic and inorganic acids and bases. Pharmaceutically acceptable acid addition salts include those formed from mineral acids such as: hydrochloric, hydrobromic, sulphuric, phosphoric, acid; and organic acids such as: citric, tartaric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, formic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts,

alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases, including salts of primary, secondary and tertiary amines, such as isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine and N-methyl-D-glucamine. Particularly preferred pharmaceutically acceptable salts include those formed from hydrochloric, trifluoroacetic and formic acids.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (I) are within the scope of the invention.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable derivatives.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

Preferred compounds of the invention include:
2-(5-Chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
(1E)-2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;

2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
2-(4-bromophenyl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
N-{(3S)-1-[(1S)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-2-(5-chlorothien-2-yl)ethanesulfonamide;
(1E)-N-{(3S)-1-[(1S)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-2-(5-chlorothien-2-yl)prop-1-ene-1-sulfonamide;
2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2R)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2R)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
2-(5-Chlorothien-2-yl)-*N*-methyl-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
N^2-{[2-(5-Chlorothien-2-yl)ethyl]sulfonyl}-N^2-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide;
Benzyl (3*S*)-3-[(3*S*)-3-({[2-(5-chlorothien-2-yl)ethyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoate;
Benzyl (3*S*)-3-[(3*S*)-3-({[(1*E*)-2-(5-Chlorothien-2-yl)prop-1-enyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoate;
2-(5-chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(4-chlorophenyl)-*N*-{(3*S*)-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(4-chloro-2-fluorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(4-bromophenyl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;

2-(4-chlorophenyl)-2,2-difluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(*Z*)-2-(4-chlorophenyl)-2-fluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide;
2-(4-chlorophenyl)-2,2-difluoro-*N*-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(*Z*)-2-(4-chlorophenyl)-2-fluoro-*N*-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide;
(1*E*)-2-(5-Chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-3-morpholin-4-yl-1-(morpholin-4-ylcarbonyl)-3-oxopropyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
(3*S*)-3-[(3*S*)-3-({[(1*E*)-2-(5-Chlorothien-2-yl)prop-1-enyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-*N*,*N*-dimethyl-4-morpholin-4-yl-4-oxobutanamide;
2-(4-bromophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
Ethyl *N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate;
Methyl *N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate;
N-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycine;
2-(5-chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-3-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(5-chlorothien-2-yl)-N-methyl-*N* -{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
N^2-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-N^1-methyl-N^2-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}glycinamide;
N^2-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-N^1,N^1-dimethyl-N^2-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}glycinamide;
(1*E*)-2-(5-chlorothien-2-yl)-3,3,3-trifluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide;
2-(2,4-dichlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(4-fluorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(4-methylphenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide;
(3*S*)-3-[(3*S*)-3-({[2-(5-Chlorothien-2-ethane]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoic acid;
and pharmaceutically acceptable derivatives thereof.

In the following preferred aspects of the invention, the Example numbers correspond to the Example numbers in the Experimental section.

In a preferred aspect, the compounds of the invention are Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46. In a more preferred aspect, the compounds of the invention are Examples 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 37, 38, 39, 40, 43, 44, 45, 46. In an even more preferred aspect, the compounds of the invention are Examples 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21, 22, 23, 24, 26, 27, 29, 30, 31, 32, 33, 37, 38, 39, 40, 43, 44, 45, 46. In an even more preferred aspect, the compounds of the invention are Examples 1, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21, 22, 23, 24, 26, 29, 30, 31, 32, 33, 37, 38, 39, 40, 43, 44, 45, 46. In a most preferred aspect, the compounds of the invention are Examples 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 17, 18, 21, 22, 23, 24, 26, 29, 30, 31, 32, 37, 38, 39, 40, 45, 46.

In another preferred aspect of the invention, the compounds of the invention are Examples 2, 3, 19, 20, 25, 28, 34, 35, 36, 41, 42. In another preferred aspect of the invention, the compounds of the invention are Examples 2, 20, 34, 35, 36, 41, 42.

Thrombin inhibitory activity is measured by the ability to inhibit human α-thrombin in a chromogenic assay using N-p-tosyl-gly-pro-lys p-nitroanilide as the chromogenic substrate, or in a fluorogenic assay using Rhodamine 110, bis-(CBZ-L-valyl-L-prolyl-L-arginine amide) as the fluorogenic substrate.

Factor Xa inhibitory activity is measured by the ability to inhibit human Factor Xa in a chromogenic assay using N-α-benzyloxycarbonyl-D-Arg-Gly-Arg-p-nitroanilide as the chromogenic substrate, or in a fluorogenic assay using Rhodamine 110, bis-(CBZ-glycylglycyl-L-arginine amide as the fluorogenic substrate.

Furthermore, compounds of formula (I) exhibit effective anti-coagulant activity in vitro as indicated by the APTT assays described in the Examples below.

Thus, the compounds of formula (I) are useful in the treatment of clinical conditions susceptible to amelioration by administration of a thrombin inhibitor. Such conditions include acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke; in oedema and PAF mediated inflammatory diseases such as adult respiratory shock syndrome, septic shock and reperfusion damage; the

treatment of pulmonary fibrosis; the treatment of tumour metastasis; neurogenerative disease such as Parkinson's and Alzheimer's diseases; viral infection; Kasabach Merritt Syndrome; Haemolytic uremic syndrome; arthritis; osteoporosis; as anti-coagulants for extracorporeal blood in for example, dialysis, blood filtration, bypass, and blood product storage; and in the coating of invasive devices such as prostheses, artificial valves and catheters in reducing the risk of thrombus formation.

Accordingly, one aspect of present invention provides a compound of formula (I) or a physiologically acceptable derivative thereof for use in medical therapy, particularly for use in the amelioration of a clinical condition in a mammal, including a human, for which a thombin inhibitor is indicated.

In another aspect, the invention provides a method for the treatment and/or prophylaxis of a mammal, including a human, suffering from a condition susceptible to amelioration by a thrombin inhibitor which method comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

In another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of a condition susceptible to amelioration by a thrombin inhibitor.

Preferably, the condition susceptible to amelioration by a thrombin inhibitor is selected from treatment of acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke.

More preferably, the condition susceptible to amelioration by thrombin inhibitor is selected from coronary thrombosis (for example myocardial infarction and unstable angina), pulmonary embolism, deep vein thrombosis and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke.

References in this specification to treatment include prophylactic treatment as well as the alleviation of symptoms.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use as a therapeutic agent for use in medicine, particularly human medicine.

While it is possible that, for use in therapy, a compound of the present invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

In a further aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Accordingly, the present invention further provides a pharmaceutical formulation comprising at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, thereof in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition susceptible to amelioration by a thrombin inhibitor.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier and/or excipient.

The compounds for use according to the present invention may be formulated for oral, buccal, parenteral, topical, rectal, or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be

coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds according to the present invention may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds according to the present invention may be formulated for topical administration by insufflation and inhalation. Examples of types of preparation for topical administration include sprays and aerosols for use in an inhaler or insufflator, or a formulated powder for use in an inhaler.

Powders for external application may be formed with the aid of any suitable powder base, for example, lactose, talc, or starch. Spray compositions may be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as metered dose inhalers, with the use of a suitable propellant.

The compounds according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or

intramuscularly) or by intramuscular injection. Thus, for example, the compounds according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge et al, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutically acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, preferably to 1mg to 500mg of the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

No toxicological effects are expected when a compound of the present invention is administered in the above-mentioned dosage range.

The compounds of formula (I) may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. The compounds of the present invention may be used in combination with other antithrombotic drugs such as thromboxane receptor antagonists, prostacyclin mimetics, phosphodiesterase inhibitors, fibrinogen antagonists, thrombolytic drugs such as tissue plaminogen activator and streptokinase, non-steroidal anti-inflammatory drugs such as aspirin, and the like.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations

comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

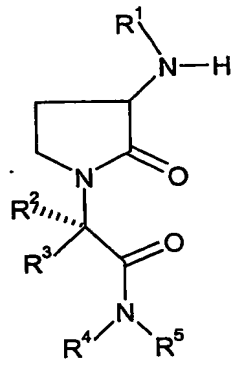
When administration is sequential, either the thrombin inhibitor or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

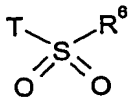
When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

The compounds of formula (I) and physiologically acceptable derivatives thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups are as defined above for compounds of formula (I) unless otherwise stated.

According to a further aspect of the present invention, there is provided a process (A) for preparing a compound of formula (I), which process comprises reacting a compound of formula (II) with a compound of formula (III):



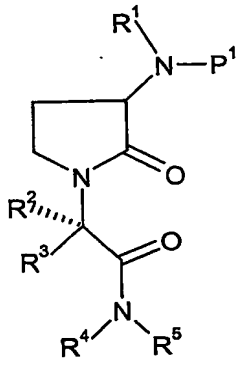
(II)



(III)

wherein T is a reactive group, such as a halide, preferably chloride. The reaction is conveniently carried out in the presence of a base, e.g. pyridine, and in a suitable solvent, e.g. acetonitrile, suitably at room temperature.

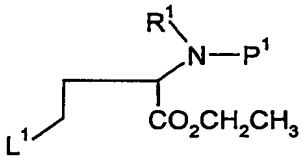
A compound of formula (II) where R^1 is hydrogen may be prepared from a compound of formula (IV)



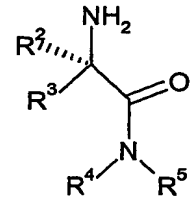
(IV)

wherein P^1 is a suitable amino protecting group, e.g. Boc (t-butyloxycarbonyl) or Cbz (benzyloxycarbonyl), by removal of the protecting group under standard conditions. For example, when P^1 represents Boc, removal of the protecting group may be effected under acidic conditions, using for example HCl in a solvent such as dioxan. For example, where P^1 represents Cbz, the protecting group may be removed by reaction with hydrogen in the presence of a metal catalyst, e.g. palladium/charcoal at atmospheric pressure. Suitably, the reaction is carried out in an alcoholic solvent, e.g. ethanol, suitably at room temperature.

A compound of formula (IV) may be prepared by reacting a compound of formula (V) with a compound of formula (VI):



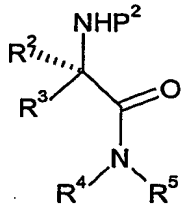
(V)



(VI)

where L^1 is a leaving group e.g. iodide, in the presence of a base e.g. triethylamine and/or 4-(dimethylamino)pyridine, in a suitable solvent e.g. acetonitrile, at elevated temperature.

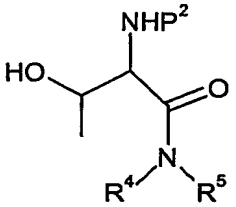
A compound of formula (VI) where R^2 is $CH(CH_3)OCH_3$ and R^3 is hydrogen, may be prepared from a compound of formula (VII)



(VII)

wherein P^2 is a suitable amino protecting group, e.g. Boc, by removal of the protecting group under standard conditions. For example, when P^2 represents Boc, removal of the protecting group may be effected under acidic conditions, using for example HCl in a solvent such as dioxan.

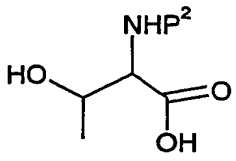
A compound of formula (VII) may be prepared from a compound of formula (VIII)



(VIII)

by reaction with trimethyloxonium tetrafluoroborate in the presence of a suitable solvent e.g. DCM, suitably at room temperature.

A compound of formula (VIII) may be prepared from a compound of formula (IX)

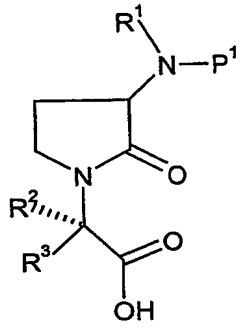


(IX)

by reaction with TBTU, N,N-diisopropyl ethylamine and morpholine in the presence of a suitable solvent e.g. DCM or DMF, suitably at room temperature.

It will be appreciated by persons skilled in the art that compounds of formula (I), may be prepared by interconversion, utilising other compounds of formula (I) which are optionally protected by standard protecting groups, as precursors. For instance, compounds of formula (I) where R^2 is $-CH_2CO_2$-benzyl, may be converted into compounds of formula (I) possessing alternative substituents at R^2, e.g. $-CH_2CO_2H$, $-CH_2C$Omorpholine, by reaction with e.g. HBr in acetic acid, suitably at room temperature, optionally followed by reaction with TBTU, N,N-diisopropyl ethylamine, and an amine e.g. morpholine, in the presence of a suitable solvent e.g. DCM or DMF, suitably at room temperature.

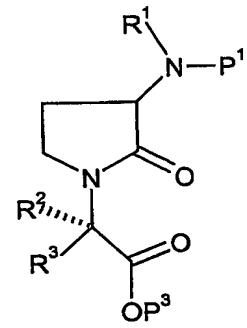
According to a process (B), a compound of formula (IV) may also be prepared from a compound of formula (X)



(X)

by reaction with TBTU, N,N-diisopropyl ethylamine and morpholine in the presence of a suitable solvent e.g. DCM or DMF, suitably at room temperature.

A compound of formula (X) may be prepared from a compound of formula (XI)

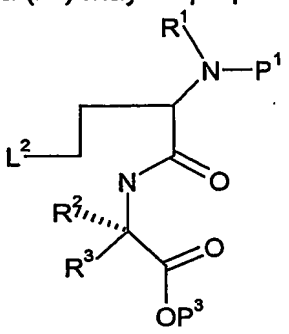


(XI)

wherein P^3 is a suitable carboxyl protecting group, e.g. t-Butyl or benzyl, by removal of the protecting group under standard conditions. For example, when P^3 represents t-Butyl, removal of the protecting group may be effected under acidic conditions, using for example trifluoroacetic acid in a solvent such as DCM. For example, when

P^3 represents benzyl, the protecting group may be removed by reaction with hydrogen in the presence of a metal catalyst, e.g. palladium/charcoal at atmospheric pressure.

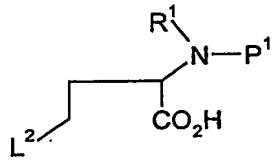
A compound of formula (XI) may be prepared from a compound of formula (XII)



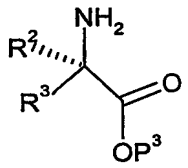
(XII)

where L^2 represents a potential leaving group, e.g. SMe, by treatment with methyl iodide, followed by ring closure with Dowex 2 x 8 400 mesh OH^- resin in a suitable solvent, e.g. MeCN (acetonitrile). Alternatively, the ring closure may be performed by treatment with potassium carbonate in a suitable solvent, e.g. MeCN.

A compound of formula (XII) may be prepared by reacting a compound of formula (XIII) with a compound of formula (XIV)



(XIII)

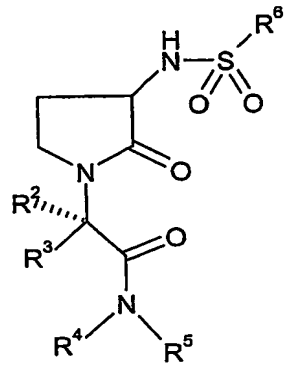


(XIV)

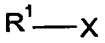
by treatment with a coupling agent, for example 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride, HOBt (1-hydroxybenzotriazole), a base, e.g. Et_3N (triethylamine), and an organic solvent, e.g. DMF or DCM, suitably at room temperature.

The various general methods described above may be useful for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product. For example, those skilled in the art will appreciate that, with the use of appropriate protecting groups, the coupling to any of groups $-R^1$, $-SO_2R^6$ or $-NR^4R^5$ can be the final step in

the preparation of a compound of formula (I). Hence, in another aspect of the invention, the final step in the preparation of a compound of formula (I) may comprise the coupling to group -R^1 by reacting a compound of formula (XV) with a compound of formula (XVI):



(XV)

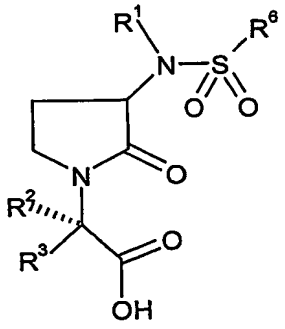


(XVI)

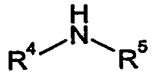
Suitably, where X is a leaving group such as a halogen atom, e.g. bromine, the reaction is carried out in the presence of a base, e.g. LiHMDS (lithium hexamethyldisilylamide), potassium carbonate or sodium carbonate. Preferably, the reaction is effected in a suitable organic solvent, e.g. THF, DMF, at a temperature from -78°C to +50°C, preferably -78°C to +20°C.

A compound of formula (XV) may be prepared under the conditions described above wherein R^1 is hydrogen.

In a further aspect of the present invention, the final step in the preparation of a compound of formula (I) may comprise the coupling to group -NR^4R^5 by reacting a compound of formula (XVII) with a compound of formula (XVIII):



(XVII)



(XVIII)

Suitably, the reaction may be carried out in the presence of a coupling agent, for example 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride, HOBt (1-hydroxybenzotriazole), a base, e.g. Et_3N (triethylamine), and an organic solvent, e.g. DCM (dichloromethane), suitably at room temperature.

A compound of formula (XVII) may be prepared by reacting a compound of formula (X) wherein P^1 is hydrogen with a compound of formula (III) under the conditions described above.

Those skilled in the art will appreciate that in the preparation of the compound of formula (I) or a solvate thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl). Examples of suitable oxygen protecting groups may include for example alky silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate.

Compounds of formulae (III), (V), (IX), (XIII), (XIV), (XVI), (XVIII) are known compounds and/or can be prepared by processes well known in the art.

Various intermediate compounds used in the above-mentioned process, including but not limited to certain compounds of formulae (II), (IV), (VI), (VII), (VIII), (X), (XI), (XII), (XV), (XVII) formulae are novel and accordingly constitute a further aspect of the present invention.

The present invention will now be further illustrated by the accompanying examples which should not be construed as limiting the scope of the invention in any way.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Examples

Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
BAST	Bis (2-methoxyethylamino) sulfur trifluoride
DCM	Dichloromethane
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
HOBT	1-Hydroxybenzotriazole
SPE	Solid phase extraction column
TBTU	o-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid

Analytical data

LCMS data was generated on a system as characterised below:
Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
Flow Rate: 3ml/min
Injection Volume: 5µl
Temp: RT
UV Detection Range: 215 to 330nM

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.

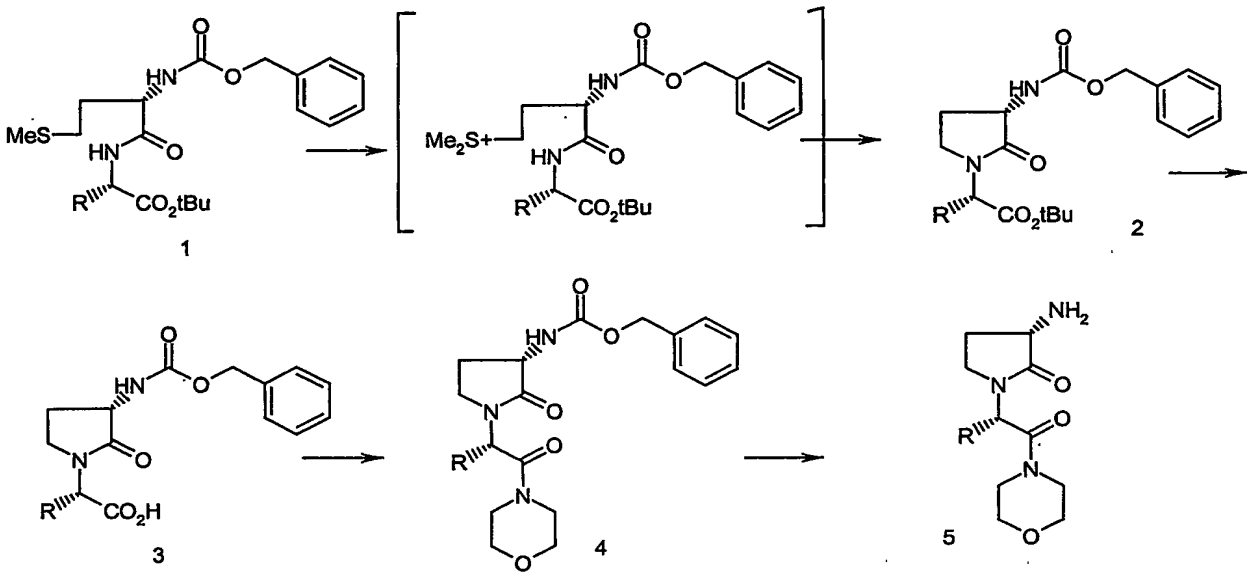
B: 95% Acetonitrile + 0.05% Formic Acid

Gradient:

Time (min)	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

Intermediates

Route 1



For R=a) Me, b) Et, c) s-Bu, d) Bn, k) iBu (to compound 2)

Intermediate 1a) *tert*-Butyl N-[(benzyloxy)carbonyl]-L-methionyl-L-alaninate

N-Benzyloxycarbonyl methionine (10g) was dissolved in DMF (200ml) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.13g) was added followed by HOBT (5.72g) and triethylamine (19.7ml). The mixture was stirred for 1h then L-alanine *tert*-butyl ester (7.7g) was added and stirring continued for 18h. The mixture was concentrated under reduced pressure and partitioned between diethyl ether and water. The separated organic phase was washed with hydrochloric acid (1N), saturated sodium bicarbonate solution and brine, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (11.9g) as an orange oil which crystallised on standing.

RT 3.11min, MH^+=410

Intermediate 1b) *tert*-Butyl (2S)-2({N-[(benzyloxy)carbonyl]-L-methionyl}amino) butanoate

A mixture of (S)-2-aminobutyric acid *tert*-butyl ester (1.96g) in DCM (50ml) was treated with N-benzyloxycarbonyl methionine (2.98g) and cooled to 10°C. N,N-Diisopropylethylamine (3.85ml) was added dropwise giving a clear solution. TBTU (3.37g) was added in portions over 2 minutes. The reaction mixture was stirred in the ice bath for 5 minutes and then allowed to warm to room temperature and stirred for 1.5 hours. The reaction mixture was stirred vigorously with saturated aqueous sodium hydrogen carbonate (70ml) for 5 minutes. The layers were separated and

the organic layer was dried and evaporated to dryness. The residue was purified by Biotage chromatography eluted with ethyl acetate:cyclohexane to give the product (3.82g).
RT

Intermediate 1c) *tert*-Butyl *N*-[(benzyloxy)carbonyl]-L-methionyl-L-isoleucinate

N-Benzyloxycarbonyl methionine (2.83g), isoleucine *tert*-butyl ester hydrochloride (2.24g), HOBT (1.35g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.92g) were stirred together in DMF (50ml) at 0°C. To the mixture was added triethylamine (2.78ml) and stirring was continued for 3.5 hours, during which the mixture was allowed to warm to room temperature. The mixture was partitioned between water (100ml) and ethyl acetate (100ml). The organic phase was diluted with a further 50ml of ethyl acetate and washed with 5% aqueous sodium hydrogen carbonate, 10% aqueous citric acid and brine (50ml each). Drying (sodium sulphate) and evaporation gave a colourless gum (4.2g) which was used without further purification.
RT 3.72min MH^+=453

Intermediate 1d) *tert*-Butyl *N*-[(benzyloxy)carbonyl]-L-methionyl-L-phenylalaninate

N-Benzyloxycarbonyl methionine (14.16g), L-phenylalanine *tert*-butyl ester hydrochloride (12.88g), HOBT (6.75g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.6g) and triethylamine (13.9ml,) were mixed in DMF (600ml) at 0°C. The mixture was stirred for 3.5 hours, during which the mixture was allowed to warm to room temperature. The mixture was partitioned between water (500ml) and ethyl acetate (500ml). The organic phase was diluted with a further 50ml of ethyl acetate and washed with 5% aqueous sodium hydrogen carbonate, 10% aqueous citric acid and brine (300ml each) to give the title compound as a white solid (23.13g).

RT 3.71min, MH^+= 487

Intermediate 1k) *tert*-Butyl *N*-[(benzyloxy)carbonyl]-L-methionyl-L-leucinate

Prepared in the manner of intermediate 1d) from N-Benzyloxycarbonyl methionine and L-leucine *tert*-butyl ester.

RT 3.55min, MH^+=453

Intermediate 2a) *tert*-Butyl (2S)-2-((3S)-3-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)propanoate

A solution of intermediate 1a) *tert*-Butyl N-[(benzyloxy)carbonyl]-L-methionyl-L-alaninate (11.9g) in acetone (75ml) was treated with methyl iodide (18ml) and stirred at room temperature for 72 hours. The reaction mixture was then concentrated under

reduced pressure to give an orange solid that was dissolved in acetonitrile (200ml). Dowex (OH^- form) resin (19.42g) was added and the mixture stirred for 18 hours at room temperature. The mixture was filtered and the resin washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford a yellow oil which was purified by Biotage chromatography (silica, eluting with cyclohexane:ethyl acetate 3:2) to give the title compound (2.92g) as a colourless oil.

Mass spectrum: Found: MH^+ 363

Intermediate 2b) *tert*-Butyl (2S)-2-((3S)-3-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)butanoate

A solution of intermediate 1b) (S)-2-((S)-2-benzyloxycarbonylamino-4-methylsulfanylbutanoylamino)butyric acid *tert*-butyl ester (4.5g) in acetone (30ml) was treated with iodomethane (6.6ml) dropwise over 5 minutes. There was no temperature rise. The reaction was stirred at room temperature, under nitrogen for 19 hours and then evaporated to give the sulfonium iodide as a sticky yellow foam (5.39g, RT 2.48min M^+ = 439). A solution of the sulfonium iodide (5.35g) in dry acetonitrile (80ml) was then treated with Dowex (OH form) resin (7.2g) and stirred at room temperature for 19 hours. The reaction mixture was filtered through celite and resin was washed with acetonitrile (50ml) and ethyl acetate (50ml). The filtrate was evaporated to dryness and purified on 2x50g SPE eluted with [3:2] to [2:1] cyclohexane:ethyl acetate to give the product as a pale yellow oil which solidified on standing (3.02g).

RT 3.34min M^+= 377.

Intermediate 2c) *tert*-Butyl (2*S*,3*S*)-2-((3*S*)-3-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)-3-methylpentanoate

Intermediate 1c) (*tert*-Butyl *N*-[(benzyloxy)carbonyl]-L-methionyl-L-isoleucinate) (4.2g) in acetone (25ml) was stirred with iodomethane (5.8ml) at room temperature for 18 hours. Evaporation of the solvent gave the sulfonium salt as a foam which was used without further purification.This was stirred in acetonitrile (80ml) for 18hours with Dowex (OH form) resin (7.5g). The suspension was filtered, the resin washed with acetonitrile and the combined filtrates evaporated. The product was purified by silica gel chromatography (Biotage, ethyl acetate:cyclohexane, 1:3) to afford the product as an oil which became a white solid on standing (2.10g). RT 3.60min MH^+=405, $M+NH_4^+$=422,

Intermediate 2d) *tert*-Butyl (2S)-2-((3S)-3-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)-3-phenyl-propanoate

To a solution of intermediate 1d) *tert*-Butyl *N*-[(benzyloxy)carbonyl]-L-methionyl-L-phenylalaninate (12.15g) in acetone (70ml) was added iodomethane (15.6ml). After

overnight stirring the solvents were evaporated giving the crude sulfonium salt (15.7g) as a foam which was used directly. This was stirred in acetonitrile (200ml) with Dowex (OH form) resin (19.4g) for 18hours. The resin was filtered off and washed with 3 portions of acetonitrile. Evaporation followed by silica gel chromatography (Biotage, ethyl acetate:cyclohexane, 1:8 to 1:4) provided the title compound as a colourless gum (9.21g).

RT 3.61min MH^+=439

Intermediate 2k) *tert*-butyl (2*S*)-2-((3*S*)-3-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)-4-methylpentanoate

Prepared in the manner as for intermediate 2d) from intermediate 1k). RT 3.42min, No ES^+ observed

Intermediate 3a) (2S)-2-((3S)-3-{[(Benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl) propanoic acid

Intermediate 2a) (*tert*-Butyl (2S)-2-((3S)-3-{[(benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)propanoate) (0.5g) was dissolved in DCM (7ml), and TFA (4.7ml) was added. The mixture was stirred at room temperature for 4 hours and then concentrated under reduced pressure to give the title compound (0.42g) as a colourless oil, which crystallised after azeotroping with toluene.

Mass spectrum: Found: MH^+ 307

Intermediate 3b) (2S)-2-((3S)-3-{[(Benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl) butanoic acid

A solution of intermediate 2b) [(S)-(2-((S)-3-benzyloxycarbonylamino-2-oxopyrrolidin-1-yl)butyric acid tert-butyl ester] (1.56g) in dry DCM (5ml) was cooled in an ice bath and treated with TFA (2.5ml) and the reaction mixture was stirred at room temperature, under nitrogen, for 2 hours. A further 2.5ml TFA was added and the reaction mixture was stirred for 1 hour. The reaction mixture was evaporated to dryness and partitioned between ethyl acetate (25ml) and brine (20ml). The layers were separated and the organic layer was washed with brine (10ml). A precipitate formed which was dissolved by adding DCM (25ml). The organic layer was separated and dried (sodium sulphate) and evaporated to dryness. The oil was mixed with diethyl ether (30ml) and water (50ml) and a thick precipitate formed which was collected by filtration and dried to give the product as colourless solid (1.17g). RT 2.73 min, MH^+=321.

Intermediate 3c) (2*S*,3*S*)-2-((3*S*)-3-{[(Benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)-3-methylpentanoic acid

Intermediate 2c) (2.05g) was stirred in dry DCM (5ml) at room temperature as TFA (5ml) was added. The mixture was stirred for 2hours and the solvents evaporated. Further DCM was added and evaporated. In order to remove residual TFA, the gum was dissolved in ethyl acetate (30ml) and was washed twice with water and with brine. Drying over sodium sulphate and evaporation gave the acid as a white solid.

RT 3.02min, MH^+=349

Intermediate 3d) (2S)-2-((3S)-3-{[(Benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl)-3-phenyl propanoic acid

Intermediate 2d) (8.84g) in DCM (30ml) was stirred with TFA (20ml) for 3.5 hours. The solvent was evaporated and the residue taken up in ethyl acetate and washed several times with water. Drying and evaporation gave the product as a white foam. RT 3.07min MH^+=383

Intermediate 4a) Benzyl (3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-ylcarbamate

Intermediate 3a) [(2S)-2-((3S)-3-{[(Benzyloxy)carbonyl]amino}-2-oxopyrrolidin-1-yl) propanoic acid] (84.5g) was dissolved in DMF (2l) and TBTU (161g) was added, followed by N,N-diisopropylethylamine (92ml) and morpholine (46ml). The mixture was stirred under nitrogen for 2.5h, and saturated aqueous ammonium chloride was added. The mixture was stirred for 15min then partitioned between water and ethyl acetate. The separated organic phase was washed with lithium chloride (10% by weight), followed by saturated sodium bicarbonate and brine. The organic layer was dried (over sodium sulphate) and concentrated under reduced pressure to give the title compound (65g) as a yellow solid.
Mass spectrum: Found: MH^+ 376

Intermediate 4b) Benzyl (3S)-1-[(1S)-1-morpholin-4-ylcarbonylpropyl]-2-oxopyrrolidin-3-ylcarbamate

A solution of intermediate 3b) (1.14g) in dry DMF (25ml) was cooled in an ice bath, under nitrogen. Morpholine (0.62ml) was added followed by N,N-diisopropylethylamine (1.24ml). TBTU (2.28g) was added in portions over 5 minutes. The pale yellow solution was stirred in the ice bath for 30 minutes and then at room temperature 16 hours. Sat. ammonium chloride (30ml) was added and then the mixture was partitioned between water (50ml) and ethyl acetate (100ml). The layers were separated and the aqueous layer was washed with ethyl acetate (50ml). The organic extracts were combined and washed with 0.5N sodium carbonate solution, 10% aq. Lithium chloride solution (2x50ml) and brine, dried (sodium sulphate) and evaporated to a gum which was purified on a 10g SPE column eluted with ethyl acetate to give the product as a colourless foam (1.16g).

RT 2.67min M^+=390.

Intermediate 4c) Benzyl (3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-ylcarbamate

To intermediate 3c) (1.81g) stirred in DMF (40ml) at room temperature was added TBTU (3.34g), N,N-diisopropylethylamine (1.81ml) and morpholine (0.95ml). After 5 hours the reaction was quenched with saturated aqueous ammonium chloride (50ml) then partitioned between ethyl acetate (150ml) and water (50ml). The aqueous phase was extracted with more EtOAc (50ml) and the combined organics washed with 2N sodium carbonate (50ml), lithium chloride (10% aq., 2 x 50ml), brine (50ml) and dried over sodium sulphate. Removal of solvent gave a gum which crystallised upon trituration with diethyl ether. The solid was filtered, washed with ether and dried (1.33g).
RT 2.95min MH^+=418

Intermediate 4d) Benzyl (3*S*)-1-[(1*S*)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-ylcarbamate

Following a similar protocol to that used for intermediate 4c), intermediate 3d) (7g), TBTU (11.75g), N,N-diisopropylethylamine (6.37ml) and morpholine (3.34ml) were stirred together in DMF (140ml) for 18 hours. Workup as for intermediate 4c) gave a gum which was purified by silica gel chromatography (Biotage, DCM then DCM:MeOH, 20:1) to afford the title compound (6.76g).

RT 2.96min MH^+=452,

Intermediate 5a) (3S)-3-Amino-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one

A mixture of intermediate 4a) (20g), 10 % palladium on carbon (2g) and ethanol (1.3l) was stirred under an atmosphere of hydrogen for 16 hours. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give the title compound (12.3g) as a pale white oil.

^{1}H NMR (D_4MeOH): δ5.05(1H, dd), 3.59(9H, m), 3.37(2H, m), 2.42(1H, m), 1.75(1H, m), 1.30(3H, d) ppm.

Intermediate 5b) (3S)-3-Amino-1-[(S)-1-(morpholin-4-ylcarbonyl)propyl]pyrrolidin-2-one

A solution of intermediate 4b) (1.14g) in ethanol (25ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10%Pd/C (50% water) (200mg) for 24 hours. The mixture was filtered through celite, washed through with ethanol (40ml) and the filtrate was evaporated to dryness. The residue was azeotroped with toluene and evaporated to a colourless oil (0.74g).

RT 1.14min, M^+=256.

Intermediate 5c) (3*S*)-3-amino-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]pyrrolidin-2-one

Intermediate 4c) (1.3g) in ethanol (25ml) was hydrogenated over 10% palladium on carbon (200mg of 50% wet catalyst) at atmospheric pressure for 18 hours. The catalyst was filtered using celite and washed with ethanol. The filtrates were evaporated giving the title compound as a colourless gum (875mg).

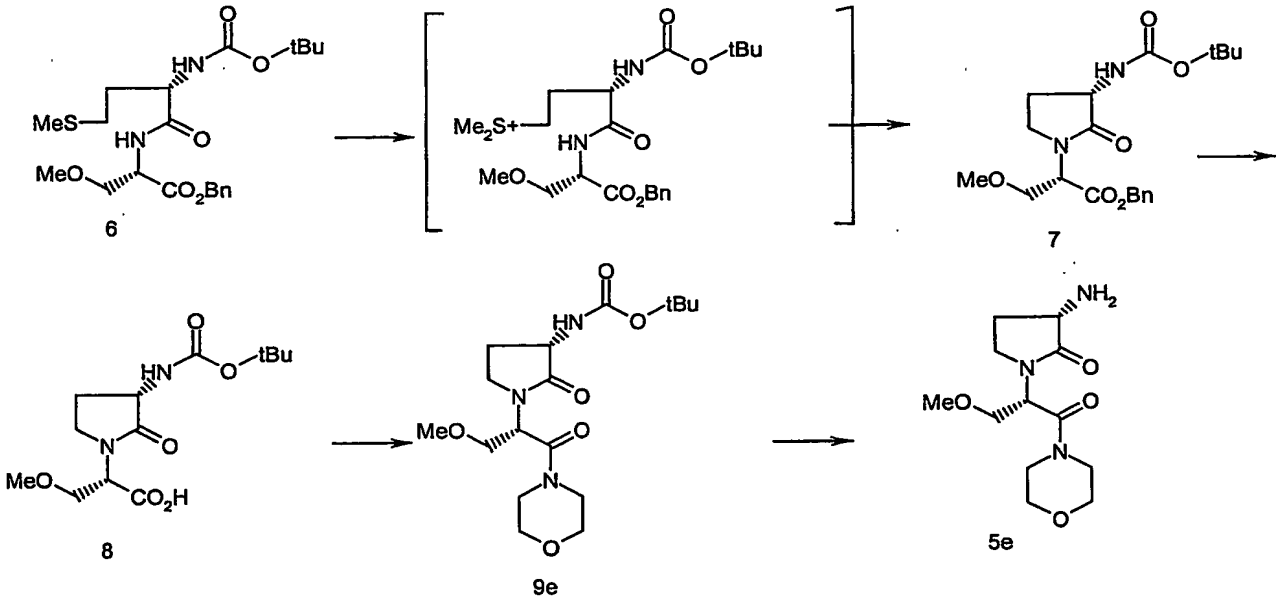
RT 1.88min, MH^+=284

Intermediate 5d) (3*S*)-3-amino-1-[(1*S*)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one

Intermediate 4d) (1.35g) in ethanol (35ml) was hydrogenated over 10% palladium on carbon (200mg) for 18 hours. After 18 hours the mixture was treated with fresh catalyst (200mg of 50% wet catalyst) and hydrogenated for a further 18 hours. The catalyst was filtered off, the filtrate evaporated, redissolved in toluene and evaporated (x2) to give the title compound as a white solid (900mg).

RT 1.89min, MH^+ 318

Route 2



Intermediate 6 Benzyl N-(tert-butoxycarbonyl)-L-methionyl-O-methyl-L-serinate

A solution of (S)-2-amino-3-methoxypropionic acid benzyl ester hydrochloride (1.40g) in dry DCM (20ml) was cooled in an ice bath under nitrogen. Boc-L-methionine (1.57g) was added followed by N,N-diisopropylethylamine (2.19ml). After stirring for 5 minutes TBTU (2.02g) was added in portions over 5 minutes. The reaction mixture was stirred for 15 minutes in the cooling bath and then stirred at room temperature for 3 hours. The reaction mixture was partitioned between DCM (25ml) and saturated sodium bicarbonate solution (40ml). The layers were separated and the aqueous layer was washed with DCM (25ml). The organic extracts were combined, washed with brine, dried (sodium sulphate) and evaporated to dryness. The oil was purified via silica gel chromatography eluted with cyclohexane:ethyl acetate (1:1) and trituration with diethyl ether/cyclohexane to give the product as a colourless solid (1.63g).

RT 3.21min M^+= 441.

Intermediate 7 Benzyl (2S)-2-{(3S)-3-[(tert-butoxycarbonyl)amino]-2-oxopyrrolidin-1-yl}-3-methoxypropanoate

A suspension of intermediate 6 [(S)-2-((S)-2-tert-butoxycarbonylamino-4-methylsulfanylbutanoylamino)-3-methoxypropionic acid benzyl ester] (1.60g) in acetone (17.5ml) was treated with iodomethane (2.3ml) dropwise over 5 minutes. The yellow solution was stirred at room temperature for 18 hours and then further iodomethane (1.5ml) was added and the reaction was stirred for 3 hours and evaporated to a yellow foam (2.22g, RT 2.42min M^+ = 455). A solution of the resulting sulfonium iodide (1.10g, 1.89 mmoles) in dry acetonitrile (15ml) was treated with Dowex (OH form) resin (2.6g) and stirred at room temperature for 18 hours. 1.5g more resin was added and reaction mixture was stirred for 2 hours. The reaction mixture was filtered through celite and resin was washed with acetonitrile (50ml) and ethyl acetate (50ml). The filtrate was evaporated to dryness and purified via silica gel chromatography eluted with hexane:ethyl acetate (2:1) to give the product as a pale yellow oil as an approximately [2:1] mixture of isomers (0.282g).

RT 3.01min M^+= 393.

Intermediate 8 (2S)-2-{(3S)-3-[(tert-Butoxycarbonyl)amino]-2-oxopyrrolidin-1-yl}-3-methoxypropanoic acid

A solution of intermediate 7 [(S)-2-((S)-3-tert-butoxycarbonylamino-2-oxopyrrolidin-1-yl)-3-methoxypropionic acid benzyl ester] (0.449g) in ethanol (10ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10%Pd/C (50% water) (300mg) for 18 hours. The mixture was filtered through celite, washed through with ethanol (40ml) and the filtrate was evaporated to dryness. The residue was azeotroped with toluene and DCM and evaporated to give the product as a colourless oil as an approximately [2:1] mixture of isomers (0.377g).

RT 2.21min, M^+= 303.

Intermediate 9e) *tert*-Butyl (3S)-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-ylcarbamate

A solution of intermediate 8 [(S)-2-((S)-3-tert-butoxycarbonylamino-2-oxopyrrolidin-1-yl)-3-methoxypropionic acid] (0.377g) in dry DMF (10ml) was cooled in an ice bath under nitrogen. Morpholine (217ul) was added followed by N,N-diisopropylethylamine (0.435ml). TBTU (0.80g) was added in portions over 5 minutes. The pale yellow solution was stirred in the ice bath for 30 minutes and then at room temperature for 18 hours. Sat. ammonium chloride (10ml) was added and then the mixture was partitioned between water (10ml) and ethyl acetate (40ml). The layers were separated and the aqueous layer was washed with ethyl acetate (2x20ml). The organic extracts were combined and washed with saturated sodium bicarbonate solution, water (10ml) and brine (10ml), dried (sodium sulphate) and evaporated to a gum which was mixed with diethyl ether and the product filtered off as a colourless solid (0.22g).

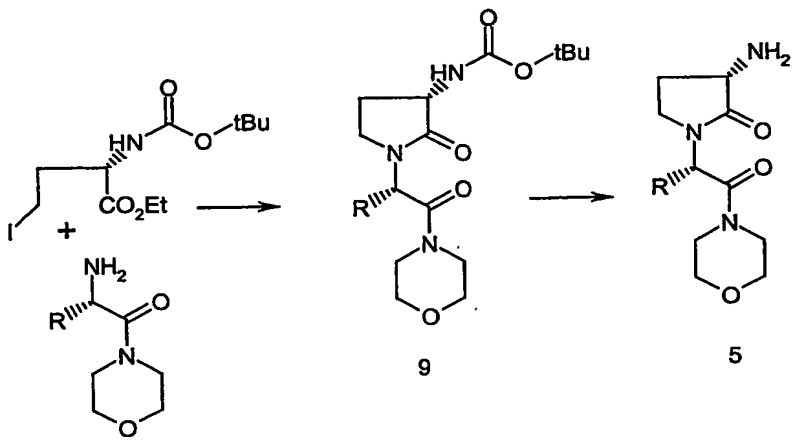
RT 2.20min M^+ = 372.

Intermediate 5e) (3S)-3-amino-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one hydrochloride.

A solution of intermediate 9e) [(S)-1-((S)-1-methoxymethyl-2-morpholin-4-yl-2-oxoxethyl)-2-oxopyrrolidin-3-yl]carbamic acid tert-butyl ester (0.215g) in dry DCM (3.5ml) was treated with 4M HCl in dioxan (0.88ml) and the solution was stirred at room temperature for 4 hours and evaporated to dryness. The residue was mixed with dichloromethane and evaporated to a colourless foam (0.208g).

RT 0.38min M^+=272.

Route 3



9 5

For f) R^2= iPr, g) R= MeOCH(CH3) j) R=CH2-(2-thienyl)

Intermediate 9f) *tert*-Butyl (3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-ylcarbamate

A solution of 2(S) ethyl 2-(tert butyloxycarbonylamino)-4-iodo butanoate* (392mg), 2-(S)-2-amino-3-methyl morpholinylbutanamide** (225mg) and triethylamine (1.1eq) in acetonitrile (5.5mL) was stirred at 80°C for 4 hours and DMAP (1.0eq) added. The mixture was then stirred at 80°C for 24 hours, solvent removed *in vacuo* and the product isolated *via* silica gel chromatography and amino-propyl SPE to give the product (230mg).

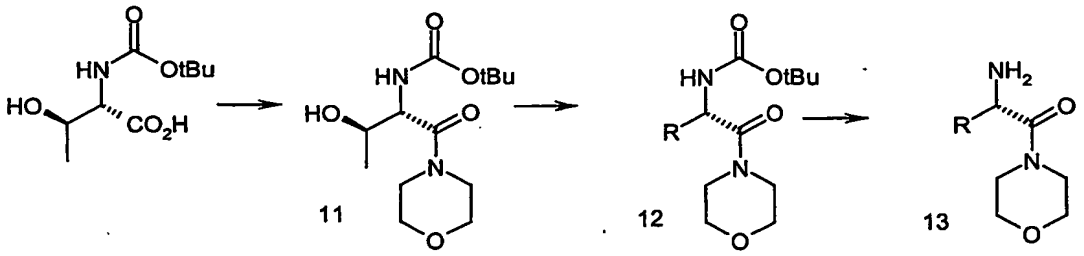
RT 2.44min, MH^+=370

* J.Med.Chem. 1994, 2950-2957

** J.Chem.Soc.Perkin Trans.1, 1975; 830-841

Intermediate 5f) (3S)-3-Amino-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]pyrrolidin-2-one hydrochloride

To a solution of intermediate 9f) (0.23g) in DCM (3mL) was added 4M HCl/dioxan solution (6.0eq) and the mixture stirred for 4 hours. The solution was reduced *in vacuo* to give the title compound. The amine was liberated from the HCl salt immediately prior to the next step *via* retention on SCX SPE column (2x10g), washing with methanol and recovery of the free amine *via* elution with methanolic ammonia (2M) and solvent removal *in vacuo* (180mg). RT 1.53min, MH^+ 270 .



For g) R= CH(CH3)OCH3) and in part j) R=(2thienyl)-CH2

Intermediate 11 *tert*-Butyl [(1S,2R)-2-hydroxy-1-(1-morpholin-4-yl-methanoyl)-propyl]carbamate

To a mixture of N-*tert*-butoxycarbonyl threonine (2.4g, 11.2mmol), N,N-diisopropylethylamine (1.2eq) and morpholine (1.0eq) in DCM (40mL) was added TBTU (1.1eq) and the mixture stirred at room temperature for 2 hours. Saturated sodium bicarbonate solution and 40mL DCM was added, the mixture stirred vigorously for 10 minutes and the layers separated. Reduction of the organic phase *in vacuo* gave the crude product that was then purified by silica gel chromatography (ethyl acetate:cyclohexane 3:1) to give the product (2.5g).
RT 2.04min MH^+=289.

Intermediate 12g) *tert*-Butyl [(1S,2R)-2-methoxyoxy-1-(1-morpholin-4-yl-methanoyl)-propyl]carbamate

A solution of intermediate 11 (1.15g, 4.0mmol) in DCM (20mL) was stirred vigorously at 0°C in the dark. To this was added Proton Sponge (1.3eq), trimethyloxonium tetrafluoroborate (1.3eq) and the mixture allowed to warm to room temperature upon which it was stirred for 8 hours. The solution was filtered, washed with 2N HCl (20mL) and reduced *in vacuo*. The resulting residue was purified *via* silica gel chromatography to give the product (0.65g).
RT 2.31min MH^+=303.

Intermediate 13g) (3*R*)-3-methoxy-1-morpholin-4-yl-1-oxobutan-2-amine HCl salt

Prepared in a similar manner to intermediate 5f) from intermediate 12h).
RT 0.46min, MH^+=203

Intermediate 9g) *tert*-butyl (3*S*)-1-[(1*S*,2*R*)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-ylcarbamate

Prepared in a similar fashion to intermediate 9f) from intermediate 13g) + 2(S) ethyl 2-(tert butyloxycarbonylamino)-4-iodo butanoate*.
RT 2.31min, MH^+=386

* J.Med.Chem. 1994, 2950-2957

Intermediate 5g) (3*S*)-3-amino-1-[(1*S*,2*R*)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]pyrrolidin-2-one

Prepared in a similar fashion to intermediate 5f), from Intermediate 9g).
RT 1.3min MH^+=286

Intermediate 12j) *tert* Butyl ((S)-2-morpholin-4-yl-2-oxo-1-thien-2-ylmethyl-ethyl)carbamate

To Boc-L-2-thienylalanine (360mg) in DCM (10ml) was added N,N-di-isopropylethylamine (0.28ml), TBTU (0.47g) and morpholine (0.13ml). The mixture was stirred for two hours, then sat. sodium bicarbonate solution (10ml) was added and the mixture stirred for 10 minutes. The organic layer was separated and evaporated in vacuo to give the title compound (480mg).
RT 2.76min, MH^+=341

Intermediate 13j) (2*S*)-1-morpholin-4-yl-1-oxo-3-thien-2-ylpropan-2-amine

Intermediate 12j) (470mg) was taken up in DCM (7ml). 4M HCl in dioxan (2ml) was added and the mixture was stirred for 2 hours. Solvent was then evaporated in vacuo, and the residue purified on an NH2-ion exchange column (eluting with methanol followed by methanol/ammonia) to give the title compound as the free base (318mg).
RT 1.47min, MH^+=241

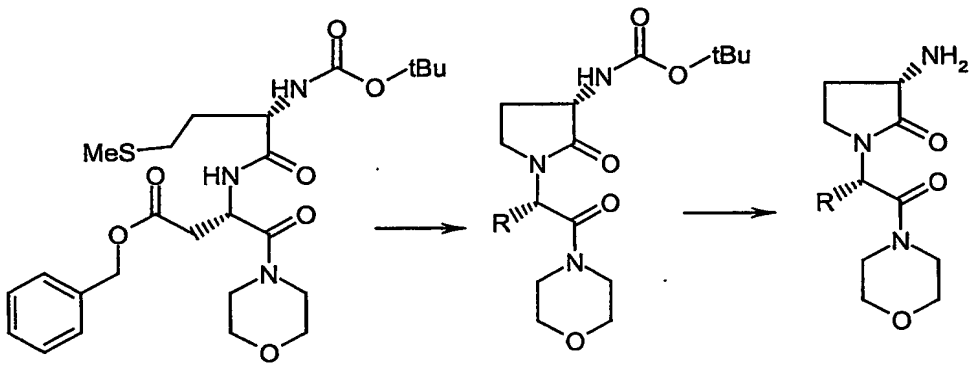
Intermediate 9j) *tert*-butyl (3*S*)-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]-2-oxopyrrolidin-3-ylcarbamate

Intermediate 13j) (316mg) and 2(S) ethyl 2-(*tert*-butyloxycarbonylamino)-4-iodo butanoate* (420mg) were stirred in acetonitrile (5ml) with triethylamine (0.18ml) and heated to 85°C. After 2 hours, DMAP (160mg) was added, and the mixture was stirred overnight at 90°C. Solvent was then evaporated in vacuo, and purified by silica gel chromatography (ethyl acetate) to give the title compound (200mg).
RT 2.79min, MH^+=424

* J.Med.Chem. 1994, 2950-2957

Intermediate 5j) (3*S*)-3-amino-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]pyrrolidin-2-one

Intermediate 9j) (190mg) was taken up in DCM (2ml). 4M HCl in Dioxan (0.68ml) was added, and the mixture stirred for 2 hours. Solvent was then evaporated in vacuo to give the title compound as the hydrochloride salt (159mg).
RT 1.74min, MH^+=324



10 9 5

9h) R=CH_2CO_2Bn 5h) R=CH_2CO_2Bn

Intermediate 10 Benzyl (S)-3-((S)-2-tert-butoxycarbonyamino-4-methylsulfonyl-butanoylamino)-4-morpholin-4-yl-4-oxo)butanoate

L-Boc-methionine (3.79g) was stirred in DMF at room temperature. TBTU (9.77g) was added followed by di-isopropylethylamine (7.9ml) and (3S)- benzyl (3*S*)-3-amino-4-morpholin-4-yl-4-oxobutanoate* (5g as the hydrochloride salt). After stirring for 3 hours, the mixture was quenched with sat. aq. Ammonium chloride (100ml) then partitioned between water (100ml) and ethyl acetate (100ml). The organic layer was washed with 2N sodium carbonate solution, 10% aq. Lithium chloride solution, then dried over sodium sulphate and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate:cyclohexane 1:1 to 2:1) gave the title compound (6.0g).
RT 3.02min, MH^+=524
* Hilpert et al, J. Med. Chem., 1994, 37, 3889-3901

Intermediate 9h) Benzyl (3*S*)-3-{(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-oxopyrrolidin-1-yl}-4-morpholin-4-yl-4-oxobutanoate

Intermediate 10 (6.0g) was stirred in acetone (35ml) and iodomethane (7.2ml) was added dropwise at room temperature. After stirring overnight, solvent was evaporated in vacuo to give the sulfonium iodide. The resulting sulfonium salt (7.6g) was not isolated but was stirred in acetonitrile (100ml). DOWEX (OH form) resin (8.3g) was added and the mixture stirred overnight. After filtration, solvent was

evaporated in vacuo to give a colourless foam. Precipitation from ethyl acetate/cyclohexane gave the title compound (4.1g).
RT 2.87min, MH^+=476

Intermediate 5h) Benzyl (3*S*)-3-[(3*S*)-3-amino-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoate hydrochloride

Intermediate 9h) (4g) was stirred in a mixture of 1,4-dioxan and 4M HCl in 1-4-dioxan for 5 hours. After evaporation of solvent in vacuo, ether (30ml) was added, and the mixture triturated then solvent re-evaporated. The ether treatment was repeated three more times to give the title compound (3.6g) as the hydrochloride salt.
RT 1.93min, MH^+ 376

Intermediate 14 2-(2-bromoethyl)-5-chlorothiophene

To a solution of 2-(5-chloro-2-thienyl)-ethanol* (12.2 g) and PPh_3 (21.4 g) in anhydrous THF (150 ml) at 0°C was added carbon tetrabromide (27.5 g). The reaction was stirred at 5 °C for 15 minutes then at room temperature for 2.5 hours. Ether was added and the reaction was then filtered and the filtrate concentrated. The resultant residue was purified by silica gel chromatography eluting with 8:1 cyclohexane: DCM to give the title compound (15g).

RT 3.50min, no Es^+ observed. NMR: ^1H, $CDCl_3$, δ 3.27 (2H, t, J = 8 Hz), δ 3.53 (2H, t, J = 8 Hz), δ 6.66 (1H, d, J = 4 Hz), δ 6.76 (1H, d, J = 4Hz).
* Schick et al., J.Amer. Chem. Soc., 70, 1948, 1646.

Intermediate 15 2-(5-chlorothien-2-yl)ethanesulfonyl chloride

To a stirred solution of intermediate 14 (14 g) in acetone (125 ml) was added an aqueous solution of sodium sulfite (10.5 g in 125 ml of H_2O). The reaction was heated at reflux for 18 hours then concentrated to yield a pearly pink solid, which was dried under vacuum at 50 °C for 18 hours. A suspension of the salt in $POCl_3$ (90ml) was heated at 150 °C for 2.5 hours. The reaction was concentrated and DCM and water added to the resultant residue. The organic portion was collected, concentrated and the resultant oil purified by silica gel chromatography (7:3 petroleum ether: toluene) to yield a brown oil (12.47g). RT = 3.33min, no Es^+ observed. NMR: ^1H, $CDCl_3$, δ 3.70 (2H, m), δ 3.22 (2H, m), δ 6.72 (1H, d, J = 4 Hz), δ 6.79 (1H, d, J = 4Hz).

Intermediate 16 1-(2-bromoethyl)-4-chlorobenzene

To a solution of 2-(4-chlorophenyl)ethanol (15 g, 95.8 mmol) in diethyl ether (225 ml) were added triphenylphosphine (31.2 g, 119 mmol) and carbon tetrabromide (38.4 g, 116 mmol). The mixture was stirred at room temperature for 16 hours, diluted with petroleum ether (bp 40-60 °C, 360 ml), and filtered. The filter cake was washed with

a mixture of diethyl ether/petroleum ether (1:1, 250 ml). The filtrate was concentrated, and the residue distilled *in vacuo* to give 1-(2-bromoethyl)-4-chlorobenzene as a colourless oil (17.35g): bp 104-105°C (0.25 mbar); ^{1}H NMR ($CDCl_3$) δ 3.12 (2H, t, *J* = 7.5Hz), 3.53 (2H, t, *J* = 7.5Hz), 7.13 (2H, d, *J* = 7.0Hz), 7.28 (2H, d, *J* = 7.0Hz); ^{13}C NMR ($CDCl_3$) δ 33.0, 39.0, 129.1 (2C), 130.4 (2C), 133.2, 137.7.

Intermediate 17 Sodium 2-(4-chlorophenyl)ethanesulfonate

Intermediate 16 (17.3 g) was dissolved in 1,4-dioxane (50 ml) and added to a solution of sodium sulfite (13.5 g) in water (170 ml). The mixture was heated under reflux for 3 hours, then evaporated to dryness. The residual solid was washed with diethyl ether, and then recrystallised from water to give the title compound (13.74 g).

Intermediate 18 2-(4-chlorophenyl)ethanesulfonyl chloride

Intermediate 17 (13.74 g) was suspended in a mixture of toluene (180 ml) and DMF (1.2 ml). Thionyl chloride (4.4 ml, 60.3 mmol) was added and the mixture was heated at 85°C for 3 hours. The mixture was cooled, then filtered through a celite pad. The filtrate was concentrated to one half the original volume, then chromatographed on silica gel using toluene as the eluent. Recrystallisation from petroleum ether gave the title compound as colourless needles (11.9g): mp 87.0-87.5°C; ^{1}H NMR ($CDCl_3$) δ 3.30-3.34 (2H, m), 3.87-3.91 (2H, m), 7.19 (2H, d, *J* = 8.0Hz), 7.34 (2H, d, *J* = 8.0Hz); ^{13}C NMR ($CDCl_3$) δ 30.2, 66.3, 129.7 (2C), 130.3 (2C), 134.0, 134.4.

Intermediate 19 Ethyl 2-(5-chlorothien-2-yl)-2-hydroxypropane-1-sulfonate

A solution of ethyl methanesulfonate (4.97g) in THF (20ml) was added dropwise to a solution of lithium hexamethyldisilylamine (42.0 ml of 1M solution in THF plus 20ml of THF) at -78°C under nitrogen and the solution was stirred for 30 minutes. A solution of 2-acetyl-5-chlorothiophene (6.75g) in THF (70ml) was added to this over fifteen minutes and the temperature maintained at -78°C for 90 minutes. The reaction was quenched with 100ml of saturated aqueous ammonium chloride and the mixture extracted with 2 x 200ml of ethyl acetate. The combined organic fractions were washed with brine; dried ($MgSO_4$) and evaporated under reduced pressure to afford a crude oil that was purified by Biotage chromatography (4 x 90g) eluted with 1:3 ether:cyclohexane. The title compound was obtained as a colourless oil (10.9g).
^{1}H NMR ($CDCl_3$): δ 6.79(1H, d), 6.73(1H, d), 4.26(2H, m), 4.14(1H, s), 3.32(1H, d), 3.52(1H, d), 1.8(3H, s), 1.36(3H, t) ppm.
RT 2.92 min, MH^+-H_2O 267 $M+NH_4^+$ 302.

Intermediate 20 Ethyl 2-(4-chlorophenyl)-2-hydroxypropane-1-sulfonate

Prepared in similar fashion to intermediate 19 from ethyl methanesulfonate and 2-acetyl-4-chlorobenzene.
RT 2.88min $M+NH_4^+$ 296

Intermediate 21 Ethyl (1E)-2-(5-chlorothien-2-yl)prop-1-ene-1-sulfonate

A solution of intermediate 19 (10.9g) in DCM (300 ml) was cooled to 0°C under nitrogen, to which was added methanesulphonic acid (15.0ml) in a dropwise fashion. After stirring for 90 min, 200ml of saturated aqueous sodium bicarbonate was added, plus 50ml of water and 50 ml of brine. The layers were separated and the aqueous layer back extracted with 100 ml of DCM; the organics were combined, washed with brine and dried over magnesium sulphate and evaporated. The crude mixture was loaded onto an 800g biotage column in 30 ml of chloroform and eluted with 15% *tert*butylmethyl ether in cyclohexane. The title compound was obtained as a white crystalline solid 2.9g (Rf 0.5 1:1 ether cyclohexane) along with 3.0 g of the unstable ethyl 2-(5-chlorothien-2-yl)prop-2-ene-1-sulfonate isomer (Rf 0.45 1:1 ether cyclohexane).
^1H NMR ($CDCl_3$): δ 7.16(1H, d), 6.92(1H, d), 6.47(1H, d) 4.26(2H, q), 2.50(3H, d), 1.42 (3H, t) ppm.
RT 3.34min MH^+ 267 $M+NH_4^+$ 284

Intermediate 22 Ethyl (1E)-2-(4-chlorophenyl)-prop-1-ene-1-sulfonate

Prepared in a similar fashion to intermediate 21 from intermediate 20 and methane sulphonic acid.
RT 3.31min $M+NH_4^+$ 278

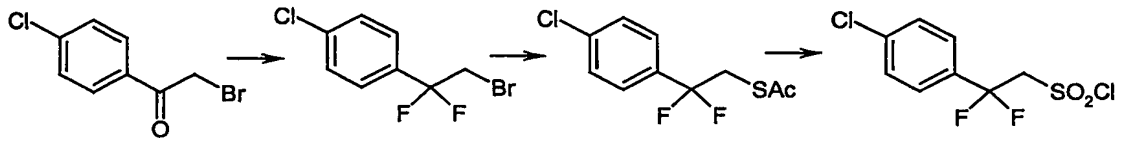
Intermediate 23 (1E)-2-(5-Chlorothien-2-yl)prop-1-ene-1-sulfonyl chloride

Tetrabutylammonium iodide (4.03g) was added to a solution of Intermediate 21 (2.9g) in acetone (180ml) under nitrogen and the solution heated under reflux for 17 hours. The solution was cooled and evaporated under reduced pressure to produce a yellow-brown solid. This was stirred in phosphorus oxychloride (30ml) at room temperature for 3.5 hours, after which the volatiles were evaporated and the residue coevaporated twice with toluene. The residue was applied, in 30ml chloroform, to 2 x 50g silica columns conditioned with chloroform. These were washed with 4x 40 ml of cyclohexane and eluted with 2 x 40 ml of 1:1 ether cyclohexane. The elution fractions were evaporated to yield the title compound as a yellow crystalline solid (2.1g).
^1H NMR ($CDCl_3$): δ 7.31(1H, d), 6.99(1H, d), 6.96(1H, q), 2.64(3H, d) ppm.
LCMS of a sample treated with 0.1 ml of 2M dimethylamine in THF afforded the clean dimethyl sulphonamide.
RT 3.22 minutes, MH^+= 266.

Intermediate 24 (1E)-2-(4-chlorophenyl)prop-1-ene-1-sulfonyl chloride

Prepared in similar fashion from intermediate 22. Treatment with dimethylamine gave the dimethylsulphonamide.

MH^+=260



25 26 27

Intermediate 25 1-(2-bromo-1,1-difluoroethyl)-4-chlorobenzene

1-(2-bromoacetyl)-4-chlorobenzene (4.0g) was stirred at 0°C in DCM (35ml). BAST (5.0ml) was added slowly and the mixture was stirred at 0°C for 1 hour then allowed to warm to room temperature and stirrd for a further 2 hours, then heated to 40°C for 4 hours. Purification by silica gel chromatography (cyclohexane:DCM 4:1) gave the title compound (3.1g).
RT 3.44 min, no Es+ seen.

Intermediate 26 *S*-[2-(4-chlorophenyl)-2,2-difluoroethyl] ethanethioate

A solution of intermediate 15 (1.5g) in DMF (27ml) was added to a solution of potassium thioacetate (1.3g) in DMF (90ml). The mixture was then stirred at 50°C for 18 hours. DCM (200ml) was added to the mixture together with water (200ml) and the layers separated. Evaporation of the organic layer in vacuo gave the title compound (1.66g).
RT 3.41 min, no Es+ seen

Intermediate 27 2-(4-chlorophenyl)-2,2-difluoroethanesulfonyl chloride

Chlorine gas was bubbled through water (250ml) in an icebath to give a yellow green solution. Intermediate 26 (536mg) was added as a chloroform solution (3ml). The reaction was stirred vigorously for 10 minutes then was allowed to warm to room temperature and was stirred for a further 5 minutes. After purging with nitrogen, the reaction mixture was extracted with chloroform. The organic portion was evaporated in vacuo to give the title compound as a white solid (562mg).
To confirm the nature of the product, a sample was treated with an excess of methylamine in THF, to give the expected sulphonamide.
RT 2.88min, M^+=270

Intermediate 28 Sodium 2-(2,4-dichlorophenyl)ethanesulphonate

1-(2-bromoethyl)-2,4-chlorobenzene * (6.8g) was mixed with sodium sulphite (3.36g) in a 4:1 mixture of water:dioxan (50ml) and heated to 140°C overnight. A further 25ml of dioxan was added and reflux continued for a further 24 hours. . The mixture was then cooled to room temperature and concentrated in vacuo. The residue was triturated with diethyl ether and dried to give the title compound.
RT 3.68min [M-Na]+=253.

* Sharafian et al., J. Het. Chem. 1994, 31, 6, 1421

Intermediate 29 2-(2,4-dichlorophenyl)ethanesulfonyl chloride

A suspension of intermediate 28 in toluene (90ml). DMF (0.58ml) was added, followed by thionyl chloride (2ml) over 5 minutes. After stirring for 4 hours, the mixture was cooled and filtered through celite, then concentrated in vacuo. The residue was purified by silica gel chromatography (toluene) to give the title compound (1.62g).

Intermediate 30 4-chloro-2-fluorostyrene

A solution of potassium t-butoxide (3.55g) was stirred in THF (40ml)at 0°C. Methyl triphenylphosphonium bromide (11.4g) was added and the mixture was stirred for 10 min at 0°C then at room temperature for 1 hour. After cooling to 10 °C, 4-chloro-2-fluorobenzaldehyde (4.2g) was added in THF (30ml) over 10 minutes and the mixture was stirred at room temperature for 3 hours. Toluene (20ml) was added and solvent volume reduced by half in vacuo. After addition of petroleum ether, the mixture was filtered and solvent removed in vacuo. The residue was purified by silica gel chromatography (toluene:petroleum ether 3:7) to give the title compound (3.26g).
RT 3.52min, no ES+

Intermediate 31 2-(4-chloro-2-fluorophenyl)ethanol

To a 0.5M solution of 9-BBN in THF (50ml) was added intermediate 30 (3.2g) in THF (30ml). The mixture was stirred at room temperature for 18 hours, then cooled to 0°C. 10N NaOH (2.5ml) was added followed by hydrogen peroxide (30%, 7.7ml) keeping T<15°C. The mixture was cautiously heated to 50 °C for 2 hours, then cooled to 10 °C and sat aq. sodium sulfite (21ml) added. The organic layer was separated, and washed with sat sodium bicarbonate solution, then brine, then dried over magnesium sulphate. Solvent was evaporated in vacuo and the residue was purified via silica gel chromatography (DCM, then DCM:ethyl acetate 9:1) to give the title compound (2.81g).

Intermediate 32 1-(2-bromoethyl)-4-chloro-2-fluorobenzene

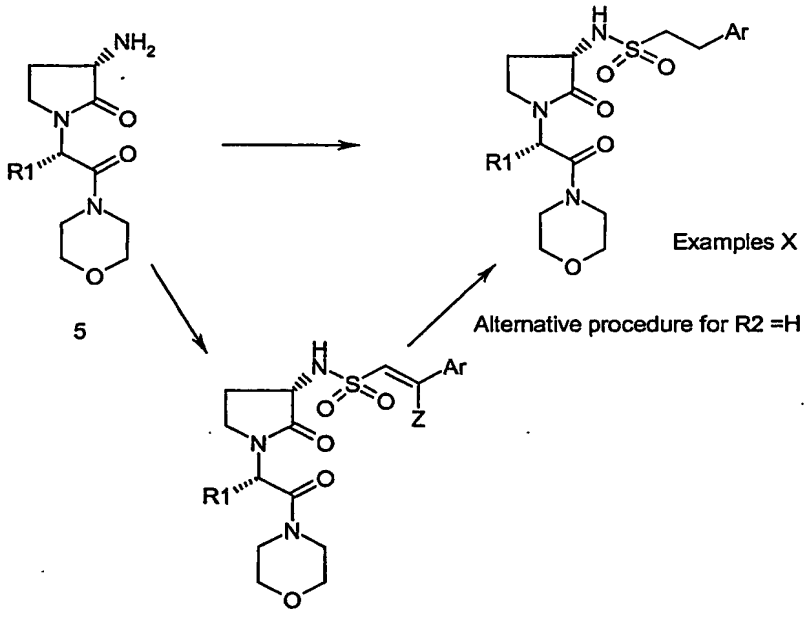
To a solution of intermediate 31 (2.8g) and 2,6-lutidine (0.44g) in ether (40ml) was added triphenylphosphine (5.2g) and carbon tetrabromide (6.4g) (with cooling to approx. 15°C). The mixture was stirred overnight at room temperature then diluted with petroleun ether (100ml) and filtered. The residue was concentrated in vacuo and then distilled under reduced pressure to give the title compound (3.76g).
BPt 85-95°C @0.19mbar

Intermediate 33 Sodium 2-(4-chloro-2-fluorophenyl)ethanesulphonate

Prepared from intermediate 32 according to the procedure for intermediate 28.
RT 3.48min, $[M-Na]^+$=237

Intermediate 34 2-(4-chloro-2-fluorophenyl)ethanesulfonyl chloride

Prepared from intermediate 33 according to the procedure for intermediate 29.

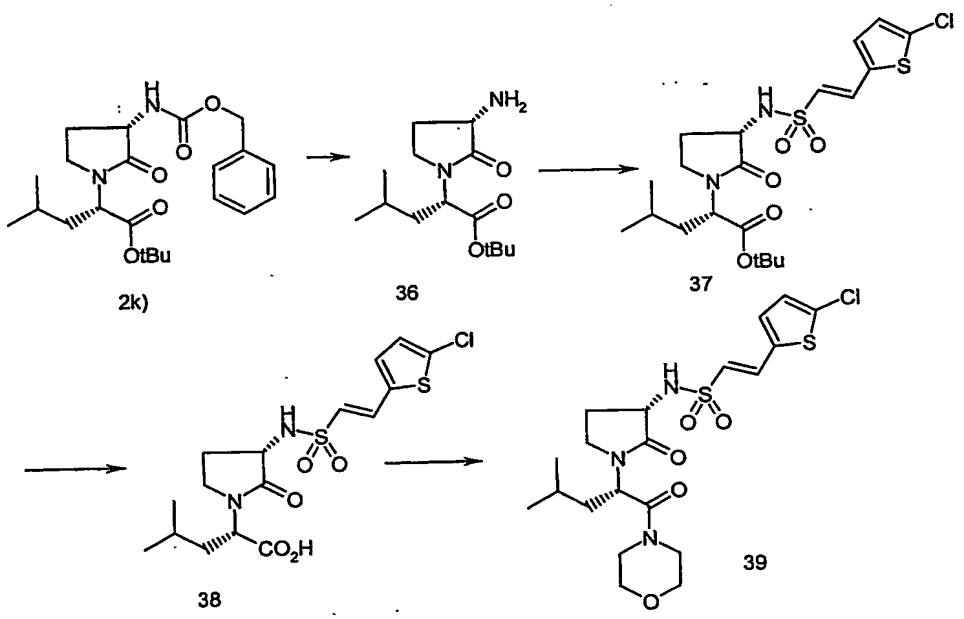


Intermediate 35) (E)-2-(5-Chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

To a solution of intermediate 5a) (3S)-3-Amino-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one (14.9g) in anhydrous acetonitrile (750ml) were added (E)-2-(5-chlorothien-2-yl)ethenesulfonyl chloride (16.5g) in acetonitrile (250ml) and pyridine

(11ml), and the mixture was stirred at room temperature for 72 hours. Saturated ammonium chloride solution was added and the resultant mixture stirred at room temperature for 30min. The mixture was concentrated under reduced pressure and the residue partitioned between chloroform and 1N HCl. The organic layer was washed with a 1:1 mixture of saturated sodium bicarbonate solution and water, and brine. The organic layer was isolated, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (19.3g) as a white solid.

RT 2.71min, MH^+=448



Intermediate 36 *tert*-Butyl (2*S*)-2-[(3*S*)-3-amino-2-oxopyrrolidin-1-yl]-4-methylpentanoate

Prepared according to the process for intermediate 5a), from intermediate 2k).

Intermediate 37 *tert*-Butyl (2*S*)-2-[(3*S*)-3-({[(*E*)-2-(5-chlorothien-2-yl)ethenyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-methylpentanoate

Prepared according to the process for intermediate 35, from intermediate 36 and (E)-2-(5-chlorothien-2-yl)ethenesulfonyl chloride.

MH^+=477

Intermediate 38 (2*S*)-2-[(3*S*)-3-({[(*E*)-2-(5-chlorothien-2-yl)ethenyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-methylpentanoic acid

Prepared according to the process for intermediate 3a), from intermediate 37.

RT 3.24min, MH^+=421

Intermediate 39 (*E*)-2-(5-chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-3-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

Prepared according to the process for intermediate 4a), from intermediate 38 and morpholine.
RT 3.07, MH^+= 490

Intermediate 40 Ethyl (1E)-2-(5-chlorothien-2-yl)-3,3,3-trifluoroprop-1-ene-1-sulfonate

A solution of ethyl (diethoxyphosphoryl)methanesulfonate (606mg) was stirred in THF at –78°C. n-Butyllithium (2.8mmol) was added as a 1.6M solution in hexanes and the mixture was stirred for 20 minutes. 2-Chloro-5-trifluoroacetylthiophene was then added as a 10ml THF solution. The mixture was stirred for a further 1 hour then was allowed to warm to room temperature. After partitioning between ethyl acetate and water, the organic portion was washed with brine, dried (sodium sulphate)and solvent evaporated in vacuo. Purification via silica gel chromatography (cyclohexane;ethyl acetate 50:1 to 19:1) gave the title compound (109mg) which eluted separately from the geometrical isomer.
RT 3.50min, MH^+=338

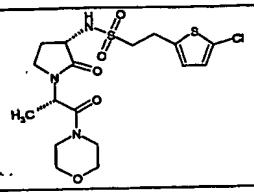
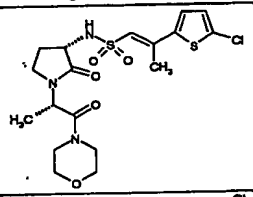
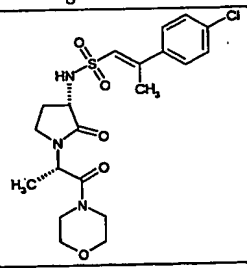
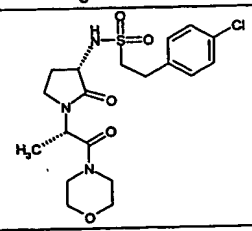
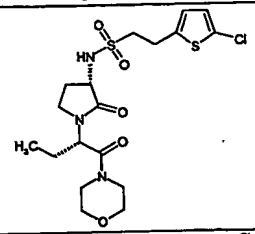
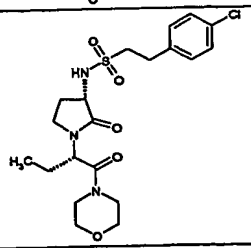
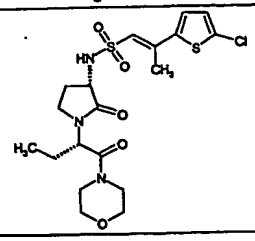
Intermediate 41 Tetra n-butylammonium (1E)-2-(5-chlorothien-2-yl)-3,3,3-trifluoroprop-1-ene-1-sulfonate

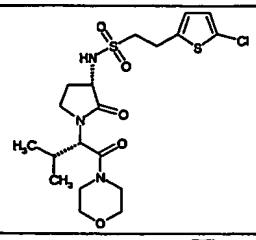
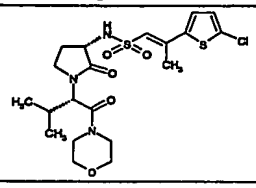
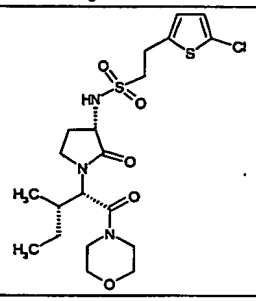
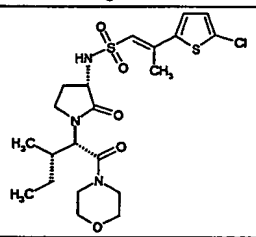
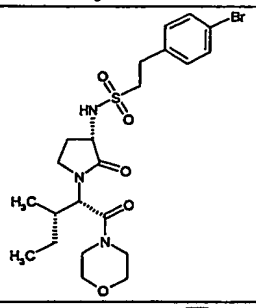
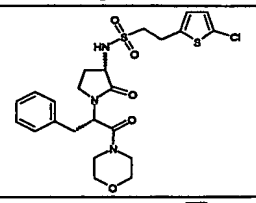
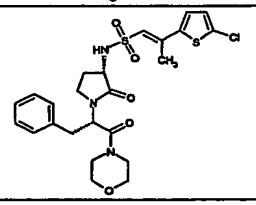
A solution of intermediate 40 (101mg) was stirred in acetone and was treated with tetra n-butylammonium iodide (117mg). The mixture was heated to reflux overnight, then solvent evaporated in vacuo to give the title compound (180mg).
RT 3.50min, No ES^+ observed

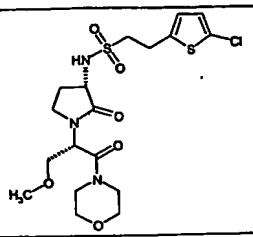
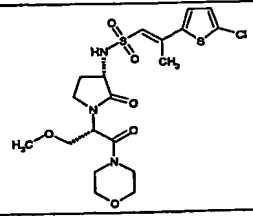
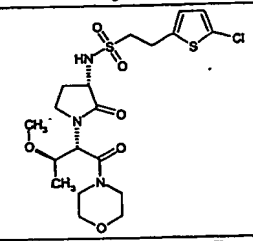
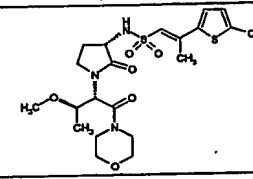
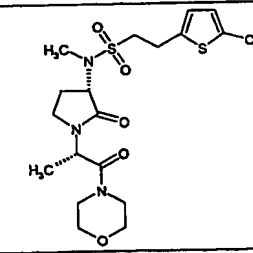
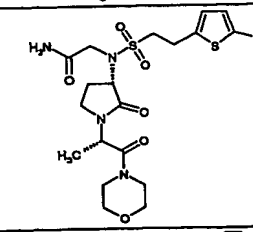
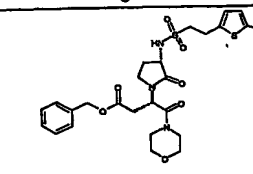
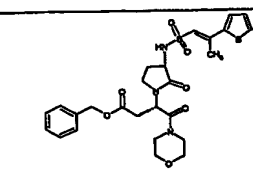
Intermediate 42 (1E)-2-(5-chlorothien-2-yl)-3,3,3-trifluoroprop-1-ene-1-sulfonyl chloride

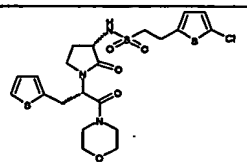
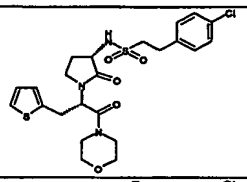
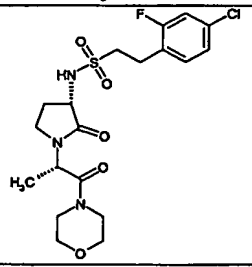
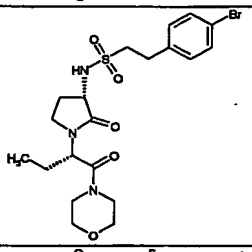
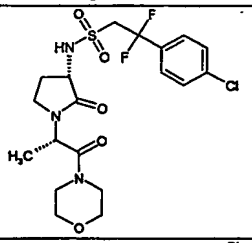
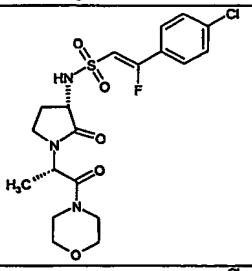
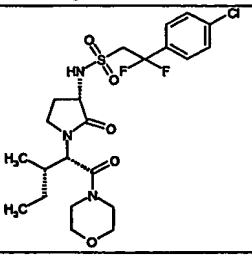
Intermediate 41 (500mg) was treated with phosphorus oxychloride (3.6ml) and stirred at room temperature for 5 hours. The reaction was then evaporated in vacuo and azeotroped (x3) with toluene in vacuo. The crude product was purified via silica gel chromatography (cyclohexane) to give the title compound (120mg).
RT 3.83min, MH^+=311

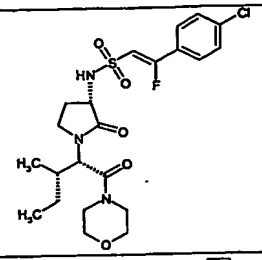
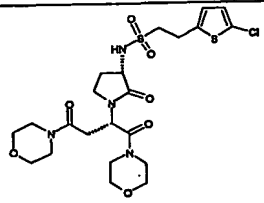
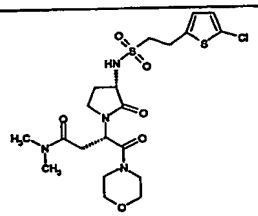
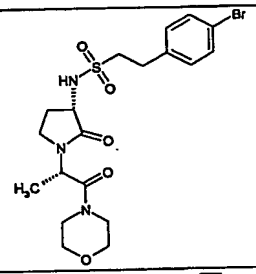
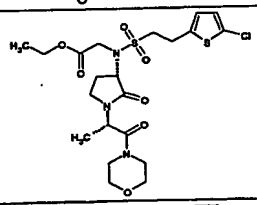
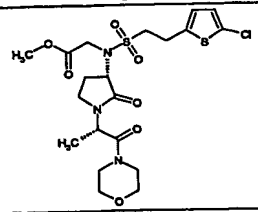
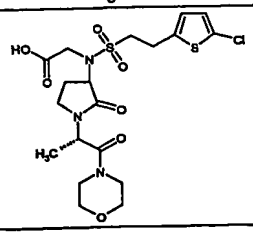
Examples

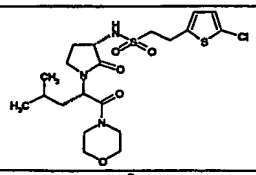
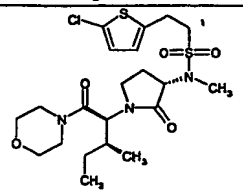
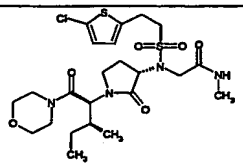
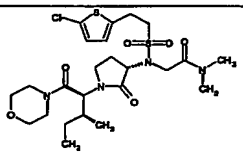
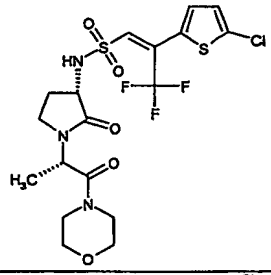
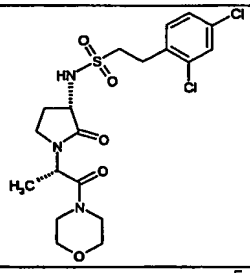
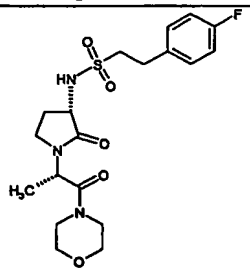
Example no		Name of compound
1		2-(5-Chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
2		(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
3		(1E)-2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
4		2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
5		2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
6		2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
7		(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

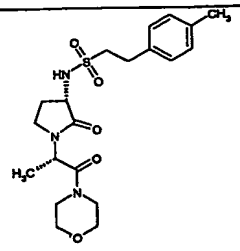
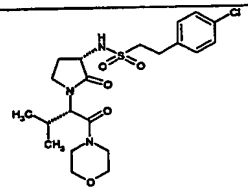
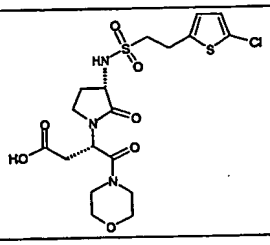
8		2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
9		(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
10		2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
11		(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
12		2-(4-bromophenyl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
13		N-{(3S)-1-[(1S)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-2-(5-chlorothien-2-yl)ethanesulfonamide
14		(1E)-N-{(3S)-1-[(1S)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-2-(5-chlorothien-2-yl)prop-1-ene-1-sulfonamide

15		2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
16		(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
17		2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2R)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
18		(1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2R)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
19		2-(5-Chlorothien-2-yl)-*N*-methyl-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
20		N^2-{[2-(5-Chlorothien-2-yl)ethyl]sulfonyl}-N^2-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide
21		Benzyl (3*S*)-3-[(3*S*)-3-({[2-(5-chlorothien-2-yl)ethyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoate
22		Benzyl (3*S*)-3-[(3*S*)-3-({[(1*E*)-2-(5-Chlorothien-2-yl)prop-1-enyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoate

23		2-(5-chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
24		2-(4-chlorophenyl)-*N*-{(3*S*)-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
25		2-(4-chloro-2-fluorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
26		2-(4-bromophenyl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
27		2-(4-chlorophenyl)-2,2-difluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
28		(*Z*)-2-(4-chlorophenyl)-2-fluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide
29		2-(4-chlorophenyl)-2,2-difluoro-*N*-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

30		(*Z*)-2-(4-chlorophenyl)-2-fluoro-*N*-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide
31		(1*E*)-2-(5-Chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-3-morpholin-4-yl-1-(morpholin-4-ylcarbonyl)-3-oxopropyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
32		(3*S*)-3-[(3*S*)-3-({[(1*E*)-2-(5-Chlorothien-2-yl)prop-1-enyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-*N*,*N*-dimethyl-4-morpholin-4-yl-4-oxobutanamide
33		2-(4-bromophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
34		Ethyl *N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate
35		Methyl *N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate
36		*N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycine

37		2-(5-chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-3-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
38		2-(5-chlorothien-2-yl)-N-methyl-*N* -{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
39		N^2-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-N^1-methyl-N^2-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}glycinamide
40		N^2-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-N^1,N^1-dimethyl-N^2-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}glycinamide
41		(1*E*)-2-(5-chlorothien-2-yl)-3,3,3-trifluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide
42		2-(2,4-dichlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
43		2-(4-fluorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

44		2-(4-methylphenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
45		2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide
46		(3*S*)-3-[(3*S*)-3-({[2-(5-Chlorothien-2-ethane]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoic acid

Example 1 2-(5-Chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

A solution of Intermediate 35 (0.1g) and chlorotris(triphenylphosphine)rhodium (1) (0.015g) in acetic acid (2ml) was stirred under a hydrogen atmosphere (60psi) at 60-70°C for 65h. The cooled reaction mixture was filtered through Celite and concentrated under reduced pressure to give a brown oil which was partially purified by silica gel chromatography (eluting with DCM, diethyl ether, ethyl acetate) to give an impure sample of the title compound. Further purification using mass directed preparative HPLC provided the title compound (0.062g) as a white solid.
RT 2.70min MH^+=450

Prepared in a similar manner was :

Example 37 2-(5-chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-3-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 39.
RT=3.16min, MH^+=492

Example 2 (1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

Intermediate 23 (190mg) was stirred in acetonitrile (15ml) at 0°C. Intermediate 5a) (120mg) and pyridine (166mg) were then added dropwise as a 5ml acetonitrile solution and the mixture was allowed to warm to room temperature., with stirrng continuing overnight. Solvent was then evaporated in vacuo and the residue partitioned between chloroform and 2N HCl/brine.. The organic layer was dried over magnesium sulphate and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate), followed by further purification via HPLC gave the title compound (9mg).

RT 2.80min, MH^+=462

Example 9 (1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

Intermediate 5f) (60mg) was dissolved in acetonitrile (1ml) at 0°C. Pyridine (44ul) and intermediate 23 (56mg) were added. The reaction was stirred for 10 minutes then at room temperature for 2 hours. Solvent was evaporated in vacuo and purified via silica gel chromatography (ethyl acetate:cyclohexane 3:1) to give the title compound (69mg).

RT 3.05 MH^+=491

Example 7 (1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

Intermediate 5b) (33mg) was dissolved in acetonitrile (0.5ml) at 0°C. Pyridine (28ul) and intermediate 23 (30mg) were added . After stirring for 15 minutes, the reaction was stirred for 1 hour. The mixture was partitioned between water (5ml) and ethyl acetate (10ml). After washing with 1N HCl and brine (5ml portions) the organics were dried (magnesium sulphate) and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate:cyclohexane 3:2) gave the title compound (51mg).
RT 3.02min MH^+=476

Example 10 2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

Intermediate 5c) (100mg) was stirred in acetonitrile (2ml) at 0°C. Pyridine (86ul) and intermediate 15 (96mg) were added in acetonitrile (1ml). The mixture was stirred for 30 minutes at 0°C then at room temperature for 3 hours. Solvent was then evaporated in vacuo. After washing with 1N HCl and brine (5ml portions) the organics were dried (magnesium sulphate) and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate:cyclohexane 1:1) gave the title compound (83mg).

RT 3.25min, MH^+=492

Example 18 (1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2R)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

Intermediate 5g) (37mg) was stirred in acetonitrile (1ml) at 0°C. Pyridine (28ul) and intermediate 23 (32mg) were added and the mixture stirred for 1 hour at 0°C then at room temperature for 3 hours. Evaporation of solvent in vacuo followed by purification via silica gel chromatography (ethyl acetate:cyclohexane 1:1) gave the title compound (28mg)
RT 2.91min, MH^+=506

Example 11 (1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

Intermediate 5c) (65mg) was stirred in acetonitrile (1.5ml) at 0°C. Pyridine (56ul) and intermediate 23 (60mg) were added in acetonitrile (1.5ml). The mixture was stirred for 30 minutes at 0°C then at room temperature for 3 hours. Solvent was then evaporated in vacuo. After washing with 1N HCl and brine (5ml portions) the organics were dried (magnesium sulphate) and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate:cyclohexane 1:1) gave the title compound (81mg).
RT 3.17min, MH^+=504

In a similar fashion were prepared the following:

Example 5 2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5b) and intermediate 15.
RT 3.17min, MH^+=465

Example 6 2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5b) and intermediate 18.
RT 3.01min, MH^+=459

Example 4 2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5a) and intermediate 18.
RT

Example 13 N-{(3S)-1-[(1S)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-2-(5-chlorothien-2-yl)ethanesulfonamide

From intermediate 5d) and intermediate 15.
RT 3.28min, MH^+=527

Example 14 (1E)-N-{(3S)-1-[(1S)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-2-(5-chlorothien-2-yl)prop-1-ene-1-sulfonamide

From intermediate 5d) and intermediate 23.
RT 3.20min, MH^+=539

Example 25 2-(4-chloro-2-fluorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From Intermediate 5a) and intermediate 34.
RT 2.78min, MH^+=462

Example 42 2-(2,4-dichlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5a) and intermediate 29.
RT 2.91min, MH^+=478

Example 43 2-(4-fluorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5a) and 2-(4-fluorophenyl)ethanesulphonyl chloride.
RT 2.59min, MH^+=428

Example 44 2-(4-methylphenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5a) and 2-(4-methylphenyl)ethanesulphonyl chloride.
RT

Example 3 (1E)-2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

From intermediate 5a) and intermediate 24.
RT 2.84min, MH^+=455

Example 12 2-(4-bromophenyl)-N-{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5c) and 2-(4-bromophenyl)ethanesulphonyl chloride.
RT 3.19min, MH^+=530/532

Example 26 2-(4-bromophenyl)-N-{(3S)-1-[(1S)-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5b) and 2-(4-bromophenyl)ethanesulphonyl chloride.
RT 2.92, MH^+=502/504

Example 33 2-(4-bromophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5a) and 2-(4-bromophenyl)ethanesulphonyl chloride
RT 2.80, MH^+=488/490

Example 41 (1*E*)-2-(5-chlorothien-2-yl)-3,3,3-trifluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

From intermediate 5a) and intermediate 42.
RT 3.09min, MH^+=516

Example 16 (1E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}prop-1-ene-1-sulfonamide

Intermediate 5e) (50mg as the hydrochloride salt) was stirred in acetonitrile (1.5ml) at 0°C. N,N-diiisopropylethylamine (28ul) was added and stirring continued for 10 minutes. Pyridine (40ul) was then added followed by intermediate 23 (50mg) and stirring continued for 15 minutes at 0°C then overnight at room temperature. The mixture was partitioned between 1N HCl (10ml) and ethyl acetate (25ml). The organic layer was then washed with brine (10ml) and dried (magnesium sulphate). Solvent was evaporated in vacuo and purification via silica gel chromatography (ethyl acetate:cyclohexane 1:2) gave the title compound (52mg).
RT 2.80min, MH^+=492

Example 15 2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-(methoxymethyl)-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

A solution of intermediate 5e) (100mg) was stirred in acetonitrile (4ml) at 0°C. N,N-diisopropylethylamine (0.14ml) was added followed by DMAP (7.9mg) and intermediate 15 (100mg). The mixture was stirred for 30 minutes, then allowed to

warm to room temperature and stirred for a further 90 minutes. The mixture was then partitioned between ethyl acetate (20ml) and 1N HCl (20ml). The organic layer was washed with saturated sodium bicarbonate solution, then dried over sodium sulphate and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate) gave the title compound (125mg).
RT 2.76min, MH^+=480

Examples 27 2-(4-chlorophenyl)-2,2-difluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide and
Example 28 (*Z*)-2-(4-chlorophenyl)-2-fluoro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

Intermediate 5a) (79mg) was stirred in acetonitrile (1ml). DMAP (7mg) and N,N-di-isopropylethylamine (0.1ml) were added, then the mixture was cooled to 0°C and intermediate 27 (77mg) was added as a 1ml acetonitrile solution. After 10 minutes the mixture was allowed to warm to room temperature and stirred overnight. The residue was partitioned between chloroform and 2N HCl, and the organic layer was passed through an ion exchange column then purified via silica gel chromatography. Further HPLC purification gave example 27 (8mg) and example 28 (1mg)
Ex 27 RT 2.83min, MH^+=480
Ex 28 RT 2.75min, MH^+=460

The following compounds were similarly prepared.

Example 29 and 2-(4-chlorophenyl)-2,2-difluoro-*N*-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide and
Example 30 (*Z*)-2-(4-chlorophenyl)-2-fluoro-*N*-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

From intermediate 5c) and intermediate 27. following HPLC purification.
Ex 29 RT 3.19min, MH^+=522
Ex 30 RT 3.13min, MH^+=502

Example 21 Benzyl (3*S*)-3-[(3*S*)-3-({[2-(5-chlorothien-2-yl)ethane]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoate

Intermediate 5h) (3.11g) was stirred in acetonitrile (40ml) and cooled to 0°C. N,N-diisopropylethylamine (4.6ml) was added followed by DMAP (300mg), and then a solution of intermediate 15 (2.03g) dropwise in acetonitrile. After stirring for 45 minutes at 0°C and 1 hour at room temperature, solvent was evaporated and the residue partitioned between ethyl acetate (100ml) and water (80ml). The organic layer was washed with 1N HCl, then saturated sodium bicarbonate solution, then

dried over sodium sulphate and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate:cyclohexane 2:1) gave the title compound (4.7g).
RT 3.24min, MH^+=584

Example 17 2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S,2R)-2-methoxy-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

Intermediate 5g) (54mg) was stirred in acetonitrile (40ml) and cooled to 0°C. N,N-diisopropylethylamine (70ul) was added followed by DMAP (5mg), and then a solution of intermediate 15 (45mg) dropwise in acetonitrile. The mixture was stirred for 1 hour at 0°C and 1 hour at room temperature, then solvent was evaporated in vacuo and the residue partitioned chloroform (10ml) and water (10ml). The organic layer was washed with 1N HCl, then sat. aqueous sodium bicarbonate, then dried over sodium sulphate and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate:cyclohexane 2:1) gave the title compound (54mg).
RT 2.88min, MH^+=494

The following were prepared in a similar fashion:

Example 23 2-(5-chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5j) and intermediate 15.
RT 3.11min, MH^+=532

Example 24 2-(4-chlorophenyl)-*N*-{(3*S*)-1-[(1*S*)-2-morpholin-4-yl-2-oxo-1-(thien-2-ylmethyl)ethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From intermediate 5j) and intermediate 18.
RT 3.13min, MH^+=526

Example 8 2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

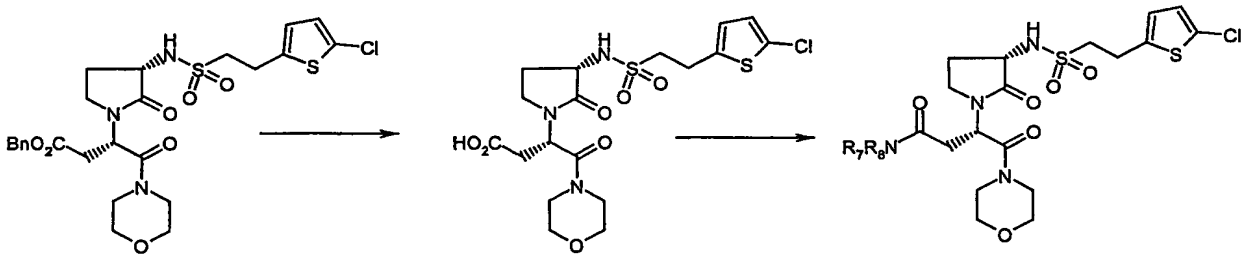
From intermediate 5f) and intermediate 15.
RT 3.06min, MH^+=478

Example 45 2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-2-methyl-1-(morpholin-4-ylcarbonyl)propyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide

From intermediate 5f) and intermediate 18.
RT 3.01min, MH^+=471

Example 22 Benzyl (3*S*)-3-[(3*S*)-3-({[(1*E*)-2-(5-chlorothien-2-yl)prop-1-enyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoate

Intermediate 5h) (100mg) was stirred in dry acetonitrile (1.5ml) at 0°C. Pyridine (76mg) was added followed by a solution of intermediate 23 (69mg) dropwise in acetonitrile. The mixture was stirred for 20 minutes at 0°C then at room temperature for 3 hours. Solvent was evaporated and the residue partitioned between ethyl acetate (5ml) and water (5ml). The organic layer was washed with 1N HCl, then saturated sodium bicarbonate, then dried over sodium sulphate and solvent evaporated in vacuo. Purification via silica gel chromatography (ethyl acetate:cyclohexane 1:1 to 2:1) gave the title compound (92mg).
RT 3.28min MH^+=596



Example 21 Example 46 Examples 31, 32

Example 46 (3*S*)-3-[(3*S*)-3-({[2-(5-Chlorothien-2-ethane]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-4-morpholin-4-yl-4-oxobutanoic acid

To example 21 (100mg) at 0°C was added 45%w/v HBr in acetic acid (2ml). The mixture was stirred for 15 minutes then allowed to warm to room temperature. After 1 hour (all starting material having dissolved) solvent was evaporated and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous phase was then acidified with 5N HCl and the resulting mixture extracted with ethyl acetate. Solvent was removed in vacuo to give the title compound (72mg).
RT 2.66min MH^+=494

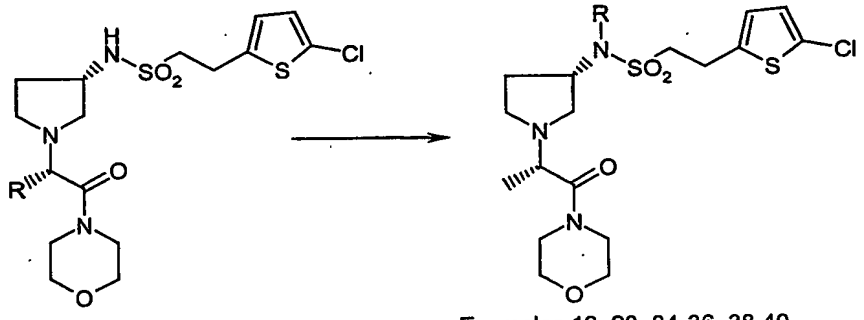
Example 31 2-(5-Chlorothien-2-yl)-*N*-{(3*S*)-1-[(1*S*)-3-morpholin-4-yl-1-(morpholin-4-ylcarbonyl)-3-oxopropyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

To example 46 (100mg) in DMF (2ml) was added TBTU (114mg), and the mixture was stirred at room temperature. Diisopropylethylamine (63ul) was added followed by morpholine (31ul) in DMF (1ml). After stirring for 2 hours the mixture was quenched with saturated ammonium chloride and then partitioned between ethyl acetate and water. The organic phase was washed with 2N sodium carbonate solution and dried over sodium sulphate. Solvent was evaporated to give the title compound (106mg).
RT 2.64min, MH+ 563

The following example was prepared in a similar manner:

Example 32 (3*S*)-3-[(3*S*)-3-({[2-(5-Chlorothien-2-yl)ethane]sulfonyl}amino)-2-oxopyrrolidin-1-yl]-*N*,*N*-dimethyl-4-morpholin-4-yl-4-oxobutanamide

From example 46 + dimethylamine.
RT 2.61min, MH^+=520



Examples 1, 10 Examples 19, 20, 34-36, 38-40

Example 19 2-(5-Chlorothien-2-yl)-*N*-methyl-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

To a solution of Example 1 (100mg) in DMF (5ml) at room temperature was added potassium carbonate (64mg) followed by methyl iodide (97mg). The mixture was stirred for 18 hours. The mixture was quenched by the addition of 2M methanolic NaOH (5ml) and DCM (5ml). The mixture was collected through a hydrophobic frit, and concentrated in vacuo to yield the title compound.
RT 3.02min, MH^+=464

Prepared in a similar manner were

Example 20 N^2-{[2-(5-Chlorothien-2-yl)ethyl]sulfonyl}-N^2-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide

Example 1+ 2-bromoacetamide.
RT 2.62min, MH^+=507

Example 34 Ethyl *N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate

Example 1 + ethyl 2-bromoacetate.
RT 3.19min, MH^+=536

Example 35 Methyl *N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate

From Example 1 + methyl bromoacetate.
RT 3.08min, MH^+=522

Example 38 2-(5-chlorothien-2-yl)-N-methyl-*N* -{(3S)-1-[(1S,2S)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}ethanesulfonamide

From Example 10 + methyl iodide.
RT 3.27min, MH^+=506

Example 39 N^2-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-N^1-methyl-N^2-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}glycinamide

From Example 10 plus N-methyl 2-bromoacetamide.
RT 3.07min, MH^+=563

Example 40 N^2-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-N^1,N^1-dimethyl-N^2-{(3*S*)-1-[(1*S*,2*S*)-2-methyl-1-(morpholin-4-ylcarbonyl)butyl]-2-oxopyrrolidin-3-yl}glycinamide

From Example 10 + N,N-dimethyl 2-chloroacetamide.
RT 3.07min M^+=577

Example 36 *N*-{[2-(5-chlorothien-2-yl)ethyl]sulfonyl}-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycine

Example 35 (60mg) was stirred in 1:1 THF:methanol (2ml). 2N NaOH (0.5ml) was added and the reaction stirred for 1 hour. The reaction was then acidified to pH 3 wth 2N HCl, and extracted with DCM. Concentration of the organic layer gave the title compound (54mg) as a mixture of isomers.
RT 2.88 and 2.94min, both MH^+=508.

Biological assays

I. Thrombin inhibitory activity

In vitro assay for inhibition of Thrombin

(A) Chromogenic assay

Example 2 was tested for Thrombin inhibitory activity as determined *in vitro* by its ability to inhibit human Thrombin in a chromogenic assay, using N-p-Tosyl-Gly-Pro-Lys-p-nitroanilide as the chromogenic substrate. The compound was diluted from a 10mM stock solution in dimethylsulfoxide at appropriate concentrations. Assay was performed at room temperature using buffer consisting of: 50mM HEPES, 150mM

NaCl, 5mM $CaCl_2$, 0.1% PEG, pH 7.4. containing human Thrombin (final conc. of 1 nM). Compound and enzyme were preincubated for 15min prior to addition of the substrate (final conc. of 100 µM). The reaction was stopped after 30min with the addition of soybean trypsin inhibitor or H-D-PHE-PRO-ARG-Chloromethylketone. BioTek EL340 or Tecan SpectraFluor Plus plate readers were used to monitor the absorbance at 405nM. To obtain IC_{50} values the data were analysed using ActivityBase® and XLfit®.

(B) Fluorogenic assay

Compounds of the present invention (Examples 1, 3-46) were tested for their Thrombin inhibitory activity as determined *in vitro* by their ability to inhibit human Thrombin in a fluorogenic assay, using Rhodamine 110, bis-(CBZ-L-valyl-L-prolyl-L-arginine amide) as the fluorogenic substrate. Compounds were diluted from a 10mM stock solution in dimethylsulfoxide at appropriate concentrations. Assay was performed at room temperature using buffer consisting of: 50mM HEPES, 150mM NaCl, 5mM $CaCl_2$, 0.1% PEG, pH 7.4. containing human Thrombin (final conc. Of 0.2 nM). Compound and enzyme were preincubated for 15min prior to addition of the substrate (final conc. of 10 µM). The reaction was stopped after 3 hrs with the addition of H-D-PHE-PRO-ARG-Chloromethylketone. An LJL- Analyst fluorimeter was used to monitor fluorescence at 485 nM excitation/535 nM emission . To obtain IC_{50} values the data were analysed using ActivityBase® and XLfit®.

All of the Examples 1-46 showed thrombin inhibitory activity. Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 45, 46 all have thrombin inhibitory Ki (nM) of less than 200. Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,21, 22, 23, 24, 26, 27, 28, 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 45, all have thrombin inhibitory Ki (nM) of less than 100. Examples 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,21, 22, 23, 24, 27, 28, 29, 32, 33, 34, 35, 38, 39, 40, 45, all have thrombin inhibitory Ki (nM) of less than 50. Examples 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 20,21, 22, 23, 24, 27, 28, 29, 33, 34, 35, 38, 39, 40, all have thrombin inhibitory Ki (nM) of less than 25. Examples 2, 7, 8, 9, 10, 11, 14, 16, 17, 18, 21, 22, 23, 38, 40, all have thrombin inhibitory Ki (nM) of less than 10.

II. Factor Xa inhibitory activity

(A) Chromogenic assay

Example 2 was tested for its Factor Xa inhibitory activity as determined *in vitro* by its ability to inhibit human Factor Xa in a chromogenic assay, using N-α-benzyloxycarbonyl-D-Arg-Gly-Arg-p-nitroanilide as the chromogenic substrate. Compounds were diluted from a 10mM stock solution in dimethylsulfoxide at appropriate concentrations. Assay was performed at room temperature using buffer consisting of: 50mM Tris-HCl, 150mM NaCl, 5mM $CaCl_2$, pH 7.4. containing human

Factor Xa (final conc. Of 0.0015 U.ml-1). Compound and enzyme were preincubated for 15min prior to addition of the substrate (final conc. of 200µM). The reaction was stopped after 30min with the addition of soybean trypsin inhibitor or H-D-PHE-PRO-ARG-Chloromethylketone. BioTek EL340 or Tecan SpectraFluor Plus plate readers were used to monitor the absorbance at 405nM. To obtain IC_{50} values the data were analysed using ActivityBase® and XLfit®.

(B) Fluorogenic assay

Compounds of the present invention (Examples 1, 3-46) were tested for their Factor Xa inhibitory activity as determined *in vitro* by their ability to inhibit human Factor Xa in a fluorogenic assay, using Rhodamine 110, bis-(CBZ-glycylglycyl-L-arginine amide as the fluorogenic substrate. Compounds were diluted from a 10mM stock solution in dimethylsulfoxide at appropriate concentrations. Assay was performed at room temperature using buffer consisting of: 50mM Tris-HCl, 150mM NaCl, 5mM $CaCl_2$, pH 7.4. containing human Factor Xa (final conc. of 0.0003U.ml-1). Compound and enzyme were preincubated for 15min prior to addition of the substrate (final conc. of 10 µM). The reaction was stopped after 3 hrs with the addition of H-D-PHE-PRO-ARG-Chloromethylketone. An LJL-Analyst fluorimeter was used to monitor fluorescence with 485 nM excitation/535 nM emission. To obtain IC_{50} values the data were analysed using ActivityBase® and XLfit®.

The ratio of inhibitory activity at thrombin compared to Factor Xa can be calculated as Factor Xa Ki (nM)/Thrombin Ki (nm)). Examples 2, 20, 34, 35, 36, 41, 42, have a ratio of inihibitory activity 0-2. Examples 3, 19, 25, 28, have a ratio of inhibitory activity of 2-5. Examples 7, 27, have a ratio of inhibitory activity of 5-10. Examples 1, 4, 16, 33, 43, 44 have a ratio of inhibitory activity of 10-25. Examples 5, 6, 8, 9, 10, 11, 12, 13, 14, 15, 17, 18, 21, 22, 23, 24, 26, 29, 30, 31, 32, 37, 38, 39, 40, 45, 46 have a ratio of inhibitory activity of greater than 25.

The ratio of inhibitory activity for prior art compounds (E)-2-(4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide and (E)-2-(5-chlorothien-2-yl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide is less than 0.04.

Method for measurement of activated partial prothrombin time (aPTT)

Blood is collected into a sodium citrate solution (ratio 9:1) to give a final concentration of 0.38% citrate. Plasma is generated by centrifugation of citrated blood samples at 1200 x g for 20 min at 4°C and stored at -20°C until use. APTT analysis is conducted using plasma pooled from 4 separate donors (2 male and 2 female).

The aPTT test is performed using the BCS Coagulation Analyzer (Dade Behring). For assay, 50 ul of plasma containing test compound at concentrations ranging from

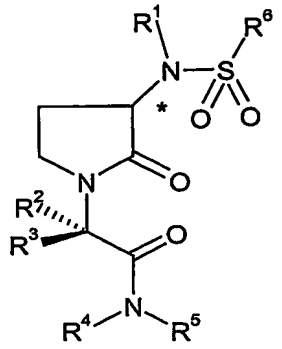
0.03 to 100 uM (made from a 100 uM stock containing 10% DMSO in plasma) is combined with 50 ul of Actin Activated Cephaloplastin Reagent (extracted from dehydrated rabbit brain; Dade Behring) and 50 ul of 0.025 M Calcium Chloride (Dade Behring). Upon addition of the reagents, absorbance at 405 nM is monitored and time to clot formation is determined (normal range for human plasma is 24-32 seconds). Results are expressed as the concentration required to extend the time to clot formation by 50%.

All Examples tested (Examples 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 26, 33, 37, 38, 39, 40, 41, 45) had 1.5x APTT values less than 30μM. Examples 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 26, 33, 37, 38, 39, 40, 45 had 1.5x APTT values less than 10μM.

The application of which this description and these claims form a part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features relating to the invention described herein. They may take the form of product, process or use claims and may include, by way of example and without limitation, the claims that follow.

CLAIMS

1. The present invention provides compounds of formula (I):



(I)

wherein:

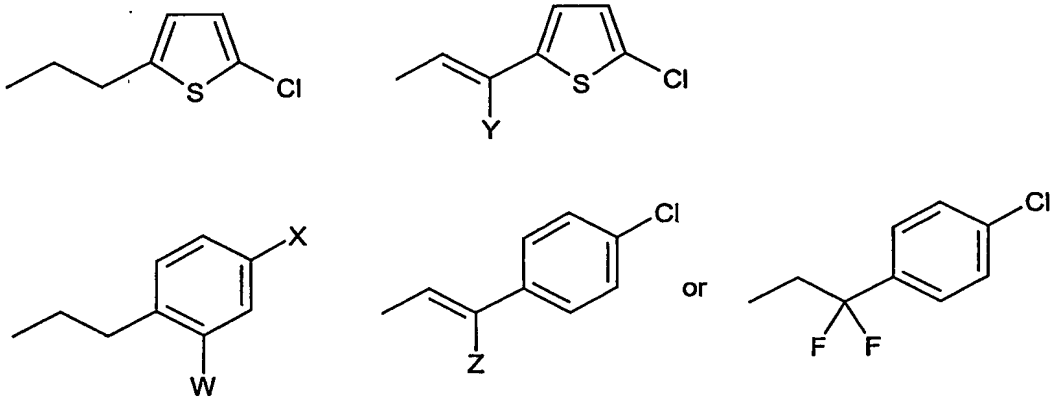
R^1 represents hydrogen, methyl, $-CH_2CO_2H$, $-CH_2CO_2C_{1-2}$alkyl, or $-CH_2CONR^7R^8$;

R^2 represents $-C_{1-4}$alkyl, $-CH_2CO_2H$, $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CON(CH_3)_2$, benzyl, $-CH_2CO_2$-benzyl, $-CH_2CO$-morpholine, or $-CH_2$-thiophene;

R^3 represents hydrogen;

R^4 and R^5 together with the nitrogen atom to which they are attached form a morpholino ring;

R^6 represents a group selected from:



wherein W represents H, Cl or F;

X represents Cl, Br, F or $-CH_3$;

Y represents CH_3 or CF_3;

Z represents $-CH_3$ or F;

R^7 and R^8 are independently hydrogen or methyl;

and pharmaceutically acceptable derivatives thereof.

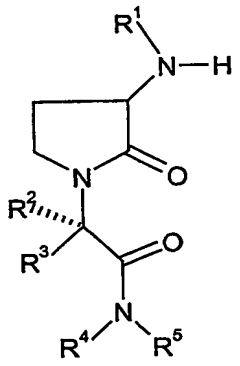
2. A compound according to claim 1 for use in therapy.

3. A pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutical carrier and/or excipient.

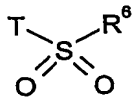
4. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a thrombin inhibitor.

5. A method of treating a patient suffering from a condition susceptible to amelioration by a thrombin inhibitor comprising administering a therapeutically effective amount of a compound according to claim 1.

6. A process for preparing a compound of formula (I) which comprises reacting a compound of formula (II) with a compound of formula (III):



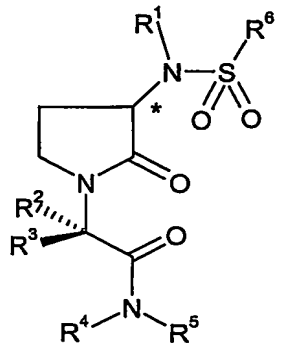
(II)



(III)

Abstract

The invention relates to compounds of formula (I):



(I)

wherein:

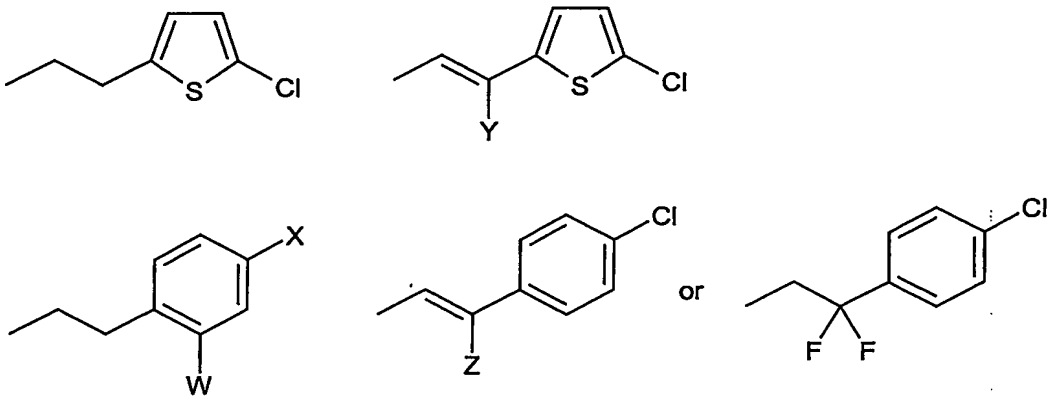
R^1 represents hydrogen, methyl, $-CH_2CO_2H$, $-CH_2CO_2C_{1\text{-}2}$alkyl, or $-CH_2CONR^7R^8$;

R^2 represents $-C_{1\text{-}4}$alkyl, $-CH_2CO_2H$, $-CH_2OCH_3$, $-CH(CH_3)OCH_3$, $-CH_2CON(CH_3)_2$, benzyl, $-CH_2CO_2$-benzyl, $-CH_2CO$-morpholine, or $-CH_2$-thiophene;

R^3 represents hydrogen;

R^4 and R^5 together with the nitrogen atom to which they are attached form a morpholino ring;

R^6 represents a group selected from:



wherein W represents H, Cl or F;

X represents Cl, Br, F or $-CH_3$;

Y represents CH_3 or CF_3;

Z represents $-CH_3$ or F;

R^7 and R^8 are independently hydrogen or methyl;

and pharmaceutically acceptable derivatives thereof, processes for their preparation, pharmaceutical compositions containing them and to their use in medicine,

particularly use in the amelioration of a clinical condition for which a thrombin inhibitor is indicated.